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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

1.	Your Reference	PB60570P1
2.	Patent application number *(The Patent office will fill in this part)*	0329462.6 19 DEC 2003
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	SMITHKLINE BEECHAM CORPORATION ONE FRANKLIN PLAZA P. O. BOX 7929 PHILADELPHIA PENNSYLVANIA 19101 UNITED STATES OF AMERICA
	Patents ADP number *(if you know it)*	5949417004
	If the applicant is a corporate body, give the country/state of its corporation	PHILADELPHIA/USA
4	Title of the invention	CHEMICAL COMPOUNDS
5	Name of your agent *(if you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	GLAXOSMITHKLINE CORPORATE INTELLECTUAL PROPERTY 980 GREAT WEST ROAD BRENTFORD, MIDDLESEX TW8 9GS, GB
	Patents ADP number *(if you know it)*	8072555006

		Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)
6.	Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months			

		Number of earlier UK application	Date of filing (day / month / year)
7.	Divisionals: etc Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)		

8.	Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?	YES

Answer YES if:

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body

Otherwise answer NO See note (d)

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheet of this form	
Description	65
Claim(s)	3
Abstract	-
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**
Signature(s) **Date:** **19 December 2003**

STEPHANIE A LEAROYD
Agent for the Applicants

12. Name and daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom **KATHERINE Y EVANS** **01 438 768611**

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Chemical Compounds

The present invention relates to certain novel compounds. In particular, the present invention relates to compounds that activate both the alpha and gamma subtypes of the human peroxisome proliferator activated receptor. The present invention also relates to methods for preparing the compounds and methods for prevention or treatment of PPAR mediated diseases or conditions.

Several independent risk factors have been associated with cardiovascular disease. These include hypertension, increased fibrinogen levels, high levels of triglycerides, elevated LDL cholesterol, elevated total cholesterol, and low levels of HDL cholesterol. HMG CoA reductase inhibitors ("statins") are useful for treating conditions characterized by high LDL-c levels. It has been shown that lowering LDL-c is not sufficient for reducing the risk of cardiovascular disease in some patients, particularly those with normal LDL-c levels. This population pool is identified by the independent risk factor of low HDL-c. The increased risk of cardiovascular disease associated with low HDL-c levels has not yet been successfully addressed by drug therapy (i.e., currently there are no drugs on the market that are useful for raising HDL-c >40%). (Bisgaier, C. L.; Pape, M. E. *Curr. Pharm. Des.* 1998, *4*, 53-70).

Syndrome X (including metabolic syndrome) is loosely defined as a collection of abnormalities including hyperinsuinlemia, obesity, elevated levels of trigycerides, uric acid, fibrinogen, small dense LDL-c particles, and plasminogen activator inhibitor 1 (PAI-1), and decreased levels of HDL-c.

NIDDM is described as insulin resistance which in turn causes anomalous glucose output and a decrease in glucose uptake by skeletal muscle. These factors eventually lead to impaired glucose tolerance (IGT) and hyperinsulinemia.

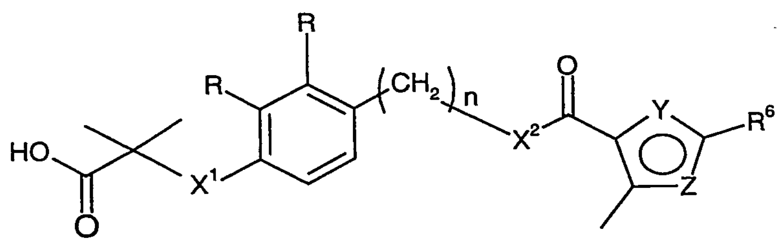
Peroxisome Proliferator Activated Receptors (PPARs) are orphan receptors belonging to the steroid/retinoid receptor superfamily of ligand-activated transcription factors. See, for example, Willson, T. M. and Wahli, W., Curr. Opin. Chem. Biol., (1997), Vol. 1, pp 235-241.

Three mammalian Peroxisome Proliferator-Activated Receptors have been isolated and termed PPAR-alpha, PPAR-gamma, and PPAR-delta (also known as NUC1 or

PPAR-beta). These PPARs regulate expression of target genes by binding to DNA sequence elements, termed PPAR response elements (PPRE). To date, PPRE's have been identified in the enhancers of a number of genes encoding proteins that regulate lipid metabolism suggesting that PPARs play a pivotal role in the adipogenic signaling cascade and lipid homeostasis (H. Keller and W. Wahli, *Trends Endocrin. Met* 291-296, 4 (1993)).

Certain compounds that activate or otherwise interact with one or more of the PPARs have been implicated in the regulation of triglyceride and cholesterol levels in animal models. See, for example, WO 01/40207, WO 01/00603, WO 97/31907, WO 02/46174 (Glaxo Group Ltd et al).

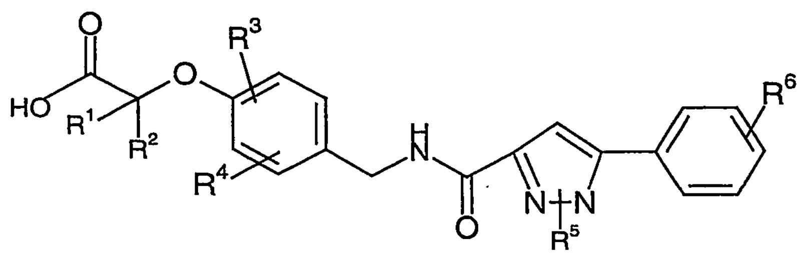
WO 01/40207 discloses compounds of the following formula:



which are stated to be useful in the treatment of PPAR mediated diseases. The compounds are particularly described as being activators of PPAR alpha and the ring defined by Y and Z are oxazole or thiazole rings.

The present inventors have prepared compounds which possess dual activity at human PPAR alpha and human PPAR gamma and as such will be useful in the treatment of human PPAR alpha and/or gamma mediated diseases, in particular dyslipidemia. In particular, the ratio of alpha to gamma activity is predicted to provide additional benefits of lipid effects provided by the gamma component when combined with PPAR alpha activity without introducing side effects which are often associated with PPAR gamma activity.

According to a first aspect of the invention there is provided a compound of formula (I) and pharmaceutically acceptable salts, solvates and hydrolysable esters thereof:



(1)

R^1 and R^2 are independently H or C_{1-3} alkyl;

R^3 and R^4 are independently H, C_{1-6} alkyl, -OC_{1-6} alkyl, halogen, OH, C_{2-6} alkenyl, CF_3;

R^5 is H, C_{1-6} alkyl or CF_3;

R^6 is C_{1-6} alkyl (optionally substituted by one or more halogens), halogen, -OC_{1-6} alkyl.

In another aspect, the present invention discloses a method for prevention or treatment of a human PPAR ("hPPAR") mediated disease or condition comprising administration of a therapeutically effective amount of a compound of this invention. hPPARmediated diseases or conditions include dyslipidemia including associated diabetic dyslipidemia and mixed dyslipidemia, syndrome X (as defined in this application this embraces metabolic syndrome), heart failure, hypercholesteremia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, inflammation, opithelial hyperproliferative diseases including eczema and psoriasis and contiditions associated with the lining and gut and regulation of appetite and food intake in subjects suffering from disorders such as obesity, bulimia, and anorexia nervosa. In particular, the compounds of this invention are useful in the treatment and prevention of cardiovascular diseases and conditions including atherosclerosis, arteriosclerosis, hypertriglyceridemia, and mixed dyslipidaemia.

In another aspect, the present invention provides pharmaceutical compositions comprising the compound of the invention, preferably in association with a pharmaceutically acceptable diluent or carrier.

In another aspect, the present invention provides the compound of the invention for use in therapy, and in particular, in human medicine.

In another aspect, the present invention provides the use of the compound of the invention for the manufacture of a medicament for the treatment of a hPPAR mediated disease or condition.

In another aspect, the present invention provides a method of treatment of a patent suffering from a hPPAR mediated disease or condition comprising the administration of therapeutically effective amount of the compound of the invention.

As used herein, "the compound of the invention" means a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or hydrolyzable ester thereof.

While hydrolyzable esters are included in the scope of this invention, the acids are preferred because the data suggests that while the esters are useful compounds, it may actually be the acids to which they hydrolyze that are the active compounds. Esters that hydrolyze readily can produce the carboxylic acid in the assay conditions or in vivo. Generally the carboxylic acid is active in both the binding and transient transfection assays, while the ester does not usually bind well but is active in the transient transfection assay presumably due to hydrolysis. Preferred hydrolysable esters are C_{1-6} alkyl esters wherein the alkyl group may be straight chain or branched chain. Methyl or ethyl esters are more preferred.

The compounds of the invention are modulators of PPAR alpha and PPAR gamma. Preferably they are agonists or partial agonists of the relevant PPAR..

The compound of formula (I) is preferably a selective dual agonist of PPAR alpha and gamma. As used herein, by "agonist", or "activating compound", or "activator", or the like, is meant those compounds which have a pKi of at least 6.0 preferably at least 7.0 to the relevant PPAR, for example hPPAR alpha in the binding assay described below, and which achieve at least 50% activation of the relevant PPAR relative to the appropriate indicated positive control in the transfection assay described below at concentrations of 10-5 M or less.

Partial agonists can be defined as compounds that transactivate the relevant PPAR, for example PPAR alpha in CV1 cells with less than 50% fold activation compared to the reference PPAR alpha full agonist in the transfection assays described below.

As used herein, a "selective dual hPPAR alpha/gamma agonist" is a hPPARalpha/gamma agonist whose EC_{50} for PPARalpha and PPAR gamma is at least 10 fold lower than its EC_{50} for PPAR delta. EC_{50} is defined in the transfection assay described below and is the concentration at which a compound achieves 50% of its maximum activity.

Preferably R^1 and R^2 are independently C_{1-3} alkyl. More preferably R^1 and R^2 are both C_{1-3} alkyl, most preferably R^1 and R^2 are both methyl.

Preferably R^4 is H.

Preferably R^3 is C_{1-3} alkyl or $-OC_{1-3}$ alkyl. Most preferably R^3 is methyl or -OCH3. R^3 is preferably ortho to the depicted Oxygen.

Preferably R^5 is methyl.

Preferably R^7 is C_{1-6} alkyl. Preferably R^7 is in the para position on the phenyl ring.

While the preferred groups for each variable have generally been listed above separately for each variable, preferred compounds of this invention include those in which several or each variable in Formula (I) is selected from the preferred, more preferred, or most preferred groups for each variable. Therefore, this invention is intended to include all combinations of preferred, more preferred, and most preferred groups.

Preferred compounds of the invention include:

Example 1:

2-[(4-{[({5-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-methylphenyl)oxy]-2-methylpropanoic acid;

Example 2:

2-methyl-2-[(2-methyl-4-{[({1-methyl-3-[4-(1-methylethyl)phenyl]-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}phenyl)oxy]propanoic acid.

Example 3:

2-{[4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-(2-propen-1-yl)phenyl]oxy}-2-methylpropanoic acid.

Example 4:

2-[(4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-propylphenyl)oxy]-2-methylpropanoic acid;

Example 5:

2-{[4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}-2-methylpropanoic acid.

Example 6:

2-{[4-{[({5-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}-2-methylpropanoic acid.

Example 7:

2-methyl-2-[(2-methyl-4-{[({1-methyl-5-[4-(2-methylpropyl)phenyl]-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}phenyl)oxy]propanoic acid

Example 8:

2-methyl-2-[(2-methyl-4-{[({1-methyl-3-[4-(2-methylpropyl)phenyl]-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}phenyl)oxy]propanoic acid;

Example 9:

2-methyl-2-{[4-{[({1-methyl-5-[4-(1-methylethyl)phenyl]-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}propanoic acid;

Example 10:

2-methyl-2-{[4-{[({1-methyl-3-[4-(1-methylethyl)phenyl]-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}propanoic acid;

Example 11:

2-[(4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-methylphenyl)oxy]-2-methylpropanoic acid;

Example 12:

2-{[4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}-2-methylpropanoic acid;

Example 13:

2-[(4-{[({5-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-methylphenyl)oxy]-2-methylpropanoic acid;

Example 14:

2-methyl-2-{[4-{[({1-methyl-5-[4-(2-methylpropyl)phenyl]-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}propanoic acid;

Example15:

2-[(4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-methylphenyl)oxy]-2-methyl propanoic acid.

Example 16:

2-[(4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}phenyl)oxy]-2-methylpropanoic acid

Example 17:

2-[(4-{[({5-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}phenyl)oxy]-2-methylpropanoic acid.

Example 18:

2-methyl-2-[(2-methyl-4-{[({1-methyl-5-[4-(1-methylethyl)phenyl]-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}phenyl)oxy]propanoic acid;

It will be appreciated by those skilled in the art that the compounds of the present invention may also be utilized in the form of a pharmaceutically acceptable salt or solvate thereof. The physiologically acceptable salts of the compounds of formula (I) include conventional salts formed from pharmaceutically acceptable inorganic or organic acids or bases as well as quaternary ammonium acid addition salts. More specific examples of suitable acid salts include hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, perchloric, fumaric, acetic, propionic, succinic, glycolic, formic, lactic, maleic, tartaric, citric, palmoic, malonic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, fumaric, toluenesulfonic, methanesulfonic, naphthalene-2-sulfonic, benzenesulfonic hydroxynaphthoic, hydroiodic, malic, steroic, tannic and the like. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable salts. More specific examples of suitable basic salts include sodium, lithium, potassium, magnesium, aluminium, calcium, zinc, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine and procaine salts. References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable salts and solvates.

The compound of the invention and its pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

While it is possible that compounds of the present invention may be therapeutically administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Accordingly, the present invention further provides for a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof together with one or more pharmaceutically acceptable carriers therefore and, optionally, other therapeutic and/or prophylactic ingredients.

The formulations include those suitable for oral, parenteral (including subcutaneous e.g. by injection or by depot tablet, intradermal, intrathecal, intramuscular e.g. by depot and intravenous), rectal and topical (including dermal, buccal and sublingual) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the compounds ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets (e.g. chewable tablets in particular for paediatric administration) each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a other conventional excipients such as binding

agents, (for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone), fillers (for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol), lubricants (for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica), disintegrants (for example, potato starch or sodium starch glycollate) or wetting agents, such as sodium lauryl sulfate. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. The tablets may be coated according to methods well-known in the art.

Alternatively, the compounds of the present invention may be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, for example. Moreover, formulations containing these compounds may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents such as sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum stearate gel or hydrogenated edible fats; emulsifying agents such as lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils) such as almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; and preservatives such as methyl or propyl p-hydroxybenzoates or sorbic acid. Such preparations may also be formulated as suppositories, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of a sterile liquid carrier, for example, water-for-injection, immediately prior to use. Extemporaneous injection

solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter, hard fat or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

The compounds may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

In addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms. Moreover, it will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general, however, doses employed for adult human treatment will typically be in the range of 0.02-5000 mg per day, preferably 1-1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day. The formulations according to the invention may contain between 0.1-99% of the active ingredient, conveniently from 30-95% for tablets and capsules and 3-50% for liquid preparations.

The compound of formula (I) for use in the instant invention may be used in combination with other therapeutic agents for example, statins and/or other lipid lowering drugs for example MTP inhibitors and LDLR upregulators. The compounds of the invention may also be used in combination with antidiabetic agents, e.g. metformin, sulfonylureas and/or PPAR gamma agonists (for example thiazolidinediones such as e.g. Pioglitazone and Rosiglitazone). The compounds may also be used in combination with antihypertensive agents such as calcium channel antagonists and ACE inhibitors. The invention thus provides in a further aspect the use of a combination comprising a compound of formula (I) with a further therapeutic agent in the treatment of a hPPAR mediated disease.

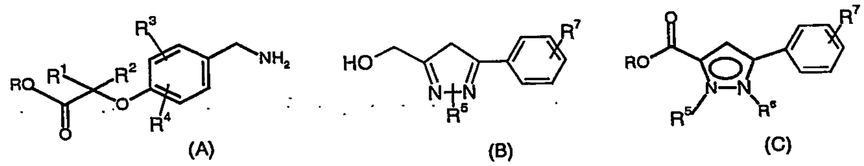
When the compounds of formula (I) are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above optimally together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation and may be formulated for administration. When formulated separately they may be provided in any convenient formulation, conveniently in such a manner as are known for such compounds in the art.

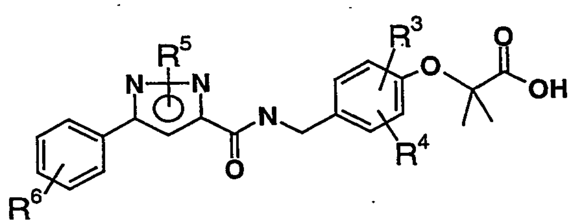
When a compound of formula (I) is used in combination with a second therapeutic agent active against the same hPPAR mediated disease, the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

Compounds of this invention may be conveniently prepared by a general process wherein a moiety like (A) is coupled to an acid (B) using a peptide coupling reaction or by acylation of (A) with an ester (C). R in formula (C) is preferably C_{1-6}alkyl. Note this synthesis is preferably carried out with the acid group of moiety A protected by R. Thus while R can be H, preferably R is C_{1-6}alkyl which can be hydrolyzed off to give an acid of Formula (I), or if readily hydrolyzable, the resulting ester can be administered.

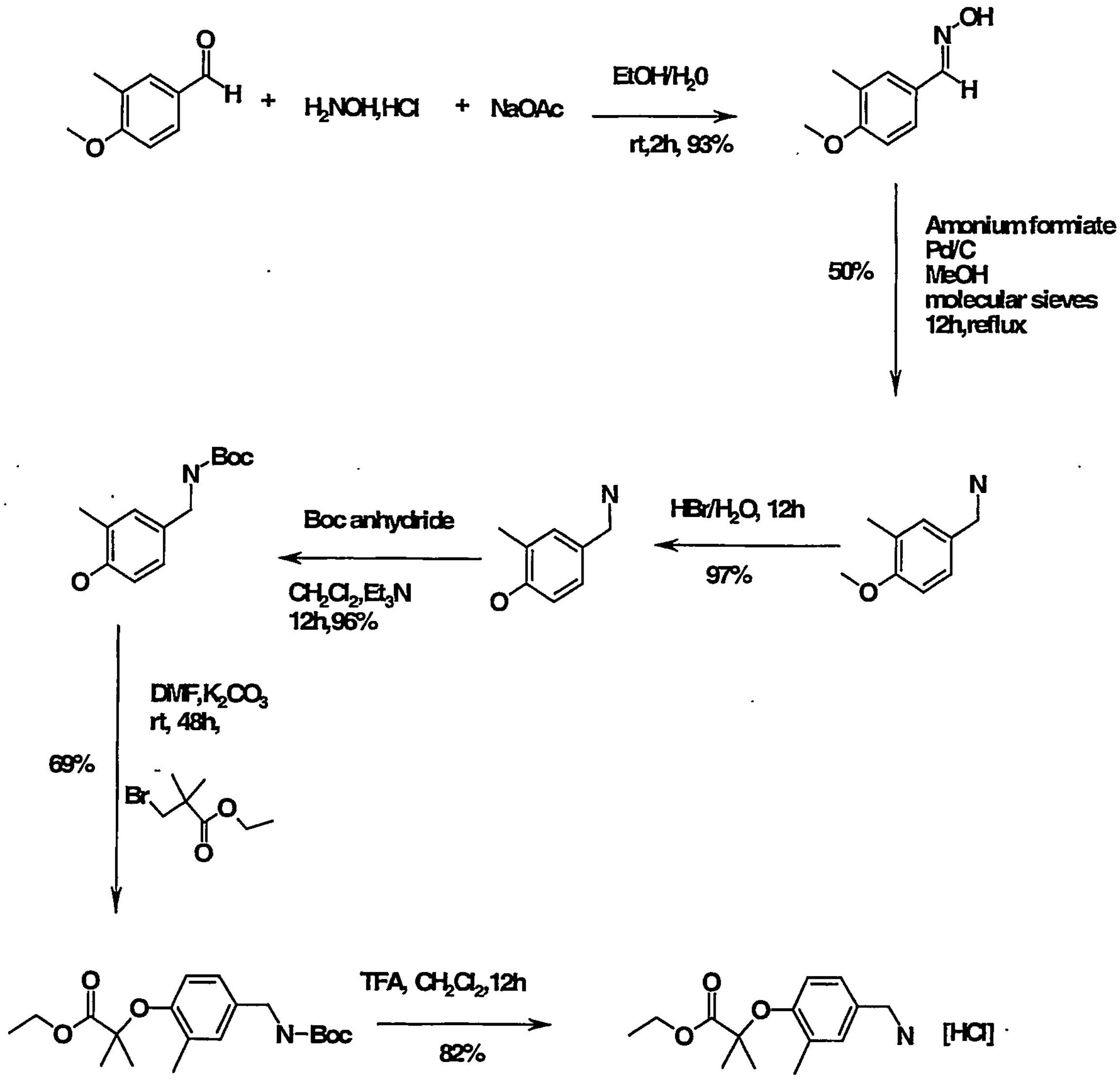


Further methods of preparing the compounds are illustrated by the schemes below. Routes of synthesis for the general structure depicted below:

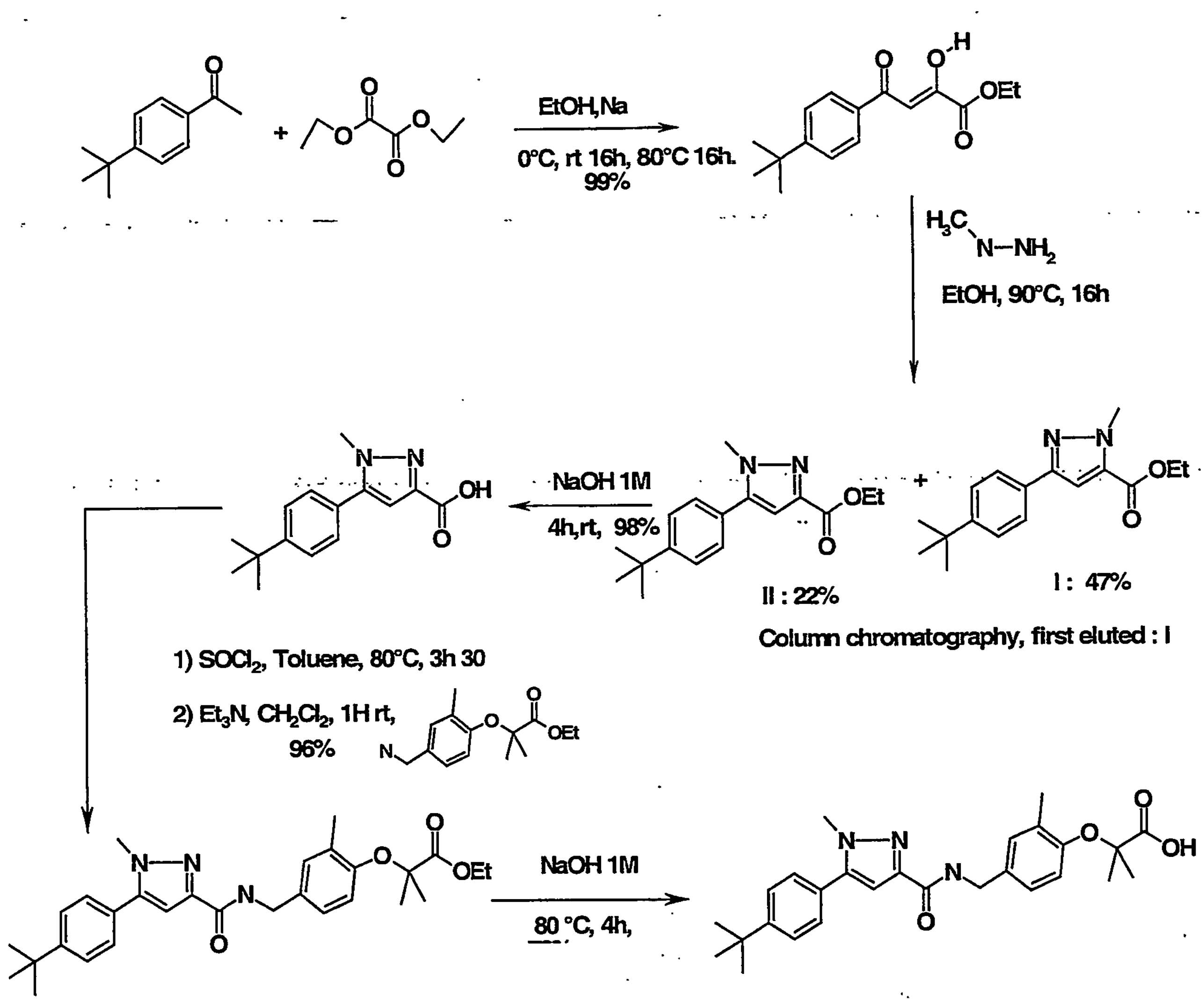
Scheme 1



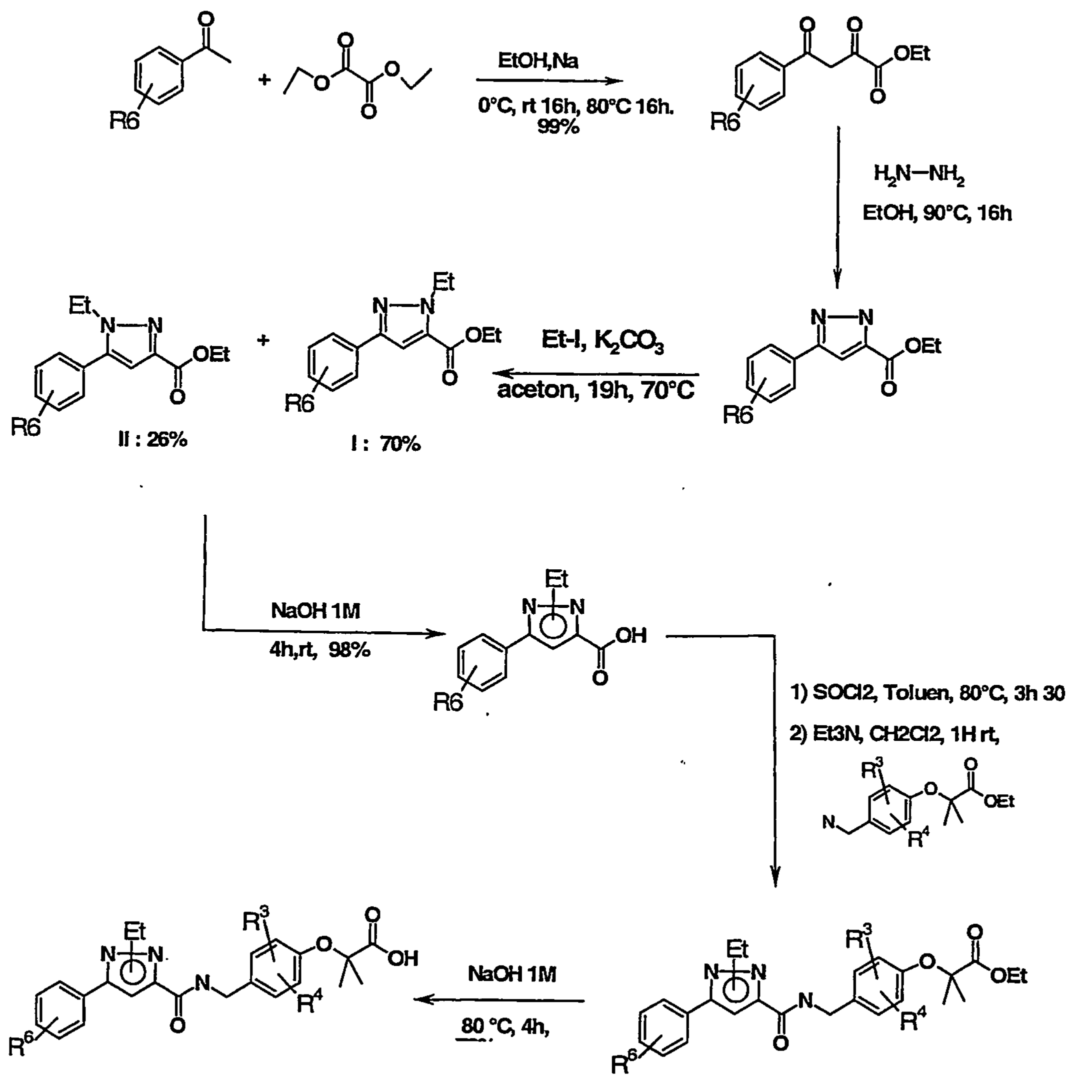
-For R^5=Me, the following general route was used (see below) :



ethyl 2-{[4-(aminomethyl)-2-methylphenyl]oxy}-2-methylpropanoate



-**For R^5=Et**, the following route was used (see below) :

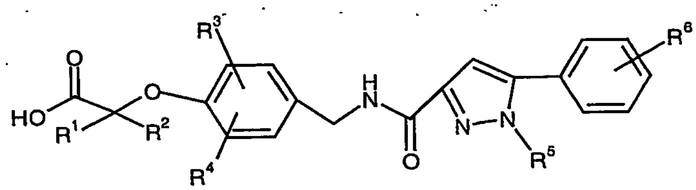


EtOH,Na
0°C, rt 16h, 80°C 16h.
99%
R6
OEt
H2N—NH2
EtOH, 90°C, 16h
Et-I, K2CO3
aceton, 19h, 70°C
II : 26%
I : 70%
NaOH 1M
4h,rt, 98%
OH
1) SOCl2, Toluen, 80°C, 3h 30
2) Et3N, CH2Cl2, 1H rt,
NaOH 1M
80 °C, 4h,

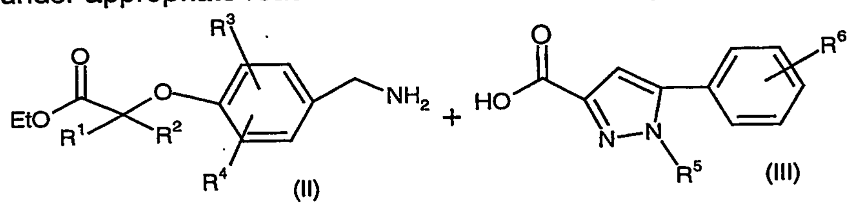
In a further process of the invention there is provided another route for the synthesis of compounds of formula (I). This is illustrated by Scheme 3 below. Scheme 3 is advantageous over Schemes 1 and 2 in that there is provided a method of achieving regio selectivity for the substituted pyrazole group as compared to Schemes 1 and 2 above which have to be resolved by chromatography.

Scheme 3

Compounds of formula (I) having the regio selectivity depicted below

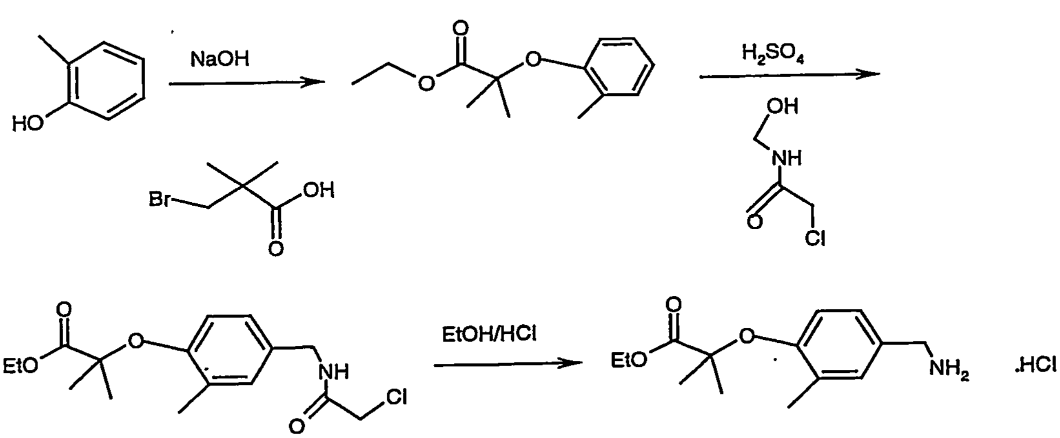


may be prepared by reacting compounds of formula (II) with compounds of formula (III)
under appropriate reaction conditions – for example DCC plus NaOH.



Compounds of formula (II) may be prepared according to Scheme 3a depicted below. This is illustrated where R^1 and R^2 are CH_3, R^3 is CH_3 and R^4 is H.

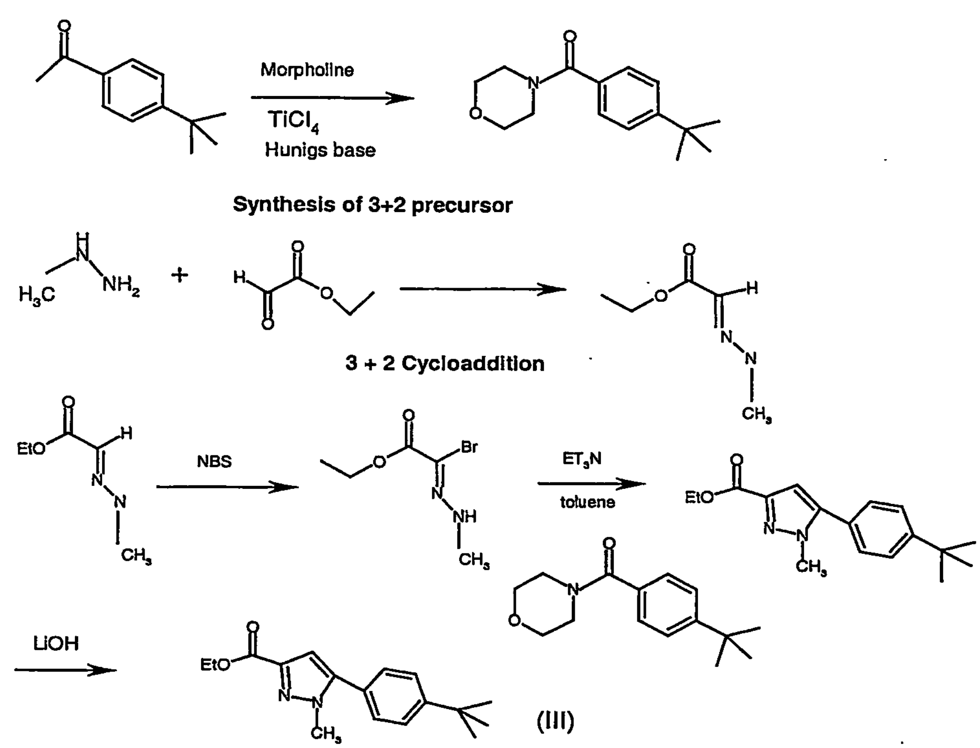
Scheme 3a



(II)

Compounds of formula (III) may be prepared accordingly to Scheme 3b depicted below. In Scheme 3b, this is illustrated for $R^6 = C(CH_3)_3$ and R^5 is CH_3.

Scheme 3b



It is submitted the above schemes are illustrative and a skilled person would be able to adapt to prepare compounds with other R^1, R^2, R^3, R^4, R^5 and R^6 groups as appropriate using these teachings and those in the specific examples below.

The invention will now be demonstrated by the following examples which should not be construed as constituting a limitation thereto.

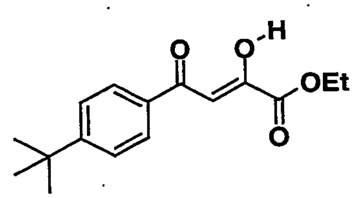
As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Unless otherwise noted, all starting materials were obtained from

commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

g (grams); mg (milligrams); L (liters); mL (milliliters); μL (microliters); mM (millimolar); mol (moles); mmol (millimoles); rt (room temperature); min (minutes); h (hours); MeOH (methanol); EEOH (ethanol); THF (tetrahydrofuran); AcOEt (ethyl acetate); Ac (acetyl).

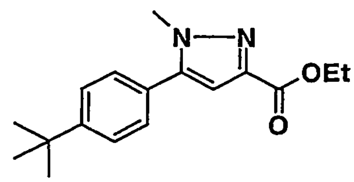
All references to ether are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade).

EXAMPLES



Intermediate 1
Ethyl (2Z)-4-[4-(1,1-dimethylethyl)phenyl]-2-hydroxy-4-oxo-2-butenoate

7.91 g of Na was added to 1L of EtOH in a 3L neck flask under nitrogen atmosphere at 0°C. A solution of 55g of p-tert-Butylacetophenone in 100mL of EtOH was added dropwise to the resulting solution and the reaction mixture was stirred for 45 min at 0°C. 50.2g of ethyl oxalate in 100 mL of EtOH was then added dropwise. The reaction mixture was stirred for 16h at rt then for 4h at 80°C. The evolution of the reaction was monitored by LC/Ms. The reaction mixture was cooled at rt and concentrated under vacuum. 1 L of ethyl acetate was added and the organic layer washed with brine, (HCl 1N) x2, and brine.
The organic layer was dried with Na_2SO_4, after filtration and evaporation under vacuum, 86g of orange oil was obtained.
^1H NMR ($CDCl_3$): δ 8.1 (d, 1H) ; 7.7 (d, 2H) ; 7.2 (s, 1H) ; 4.5 (q , 3H) ; 1.5 (m, 12H).



Intermediate 2

Ethyl 5-(4-*tert*-butylphenyl)-1-methyl-1*H*-pyrazole-3-carboxylate

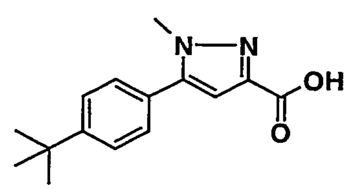
24.7 mL of methyl hydrazine.was added to a solution of 86 g of **Intermediate 1** in 1L of EtOH. The reaction mixture was heated at 90°C for 16h, cooled at rt and concentrated under vacuum. 1 L of Ethyl acetate was added and the organic layer was washed with brine, (HCl 1N) x2, and brine.

The organic layer was dried with Na_2SO_4 after filtration and evaporation, under vacuum, the solid obtained was purified on flash silica column Cyclohexane/AcOEt (95/5) first eluted then Cyclohexane/AcOEt (95/5).

First eluted: 41.3g, yield 47%.

Second eluted Intermediate 2: 19.7g yield 22%: (1H-Pyrazole-3-carboxylic acid, 1-methyl-5- [4(terBu) phenyl]-, ethyl ester)

^{1}H NMR ($CDCl_3$) : δ 7.3 (d, 2H) ; 7.1 (d, 2H) ; 6.6 (s, 1H) ; 4,2 (q,.3H) ; 3,7 (s, 3H) ; 1.2 (m, 12H).



Intermediate 3

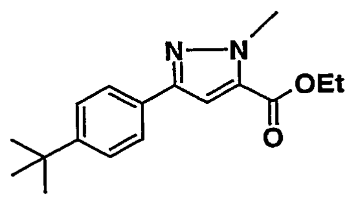
5-(4-*tert*-butylphenyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid

300 mL of EtOH and 687mL of NaOH 1N was added to a solution of 19.7 g of **Intermediate 2**, in 50 mL of THF. The reaction mixture was stirred 3h30 at rt, EtOH and THF were evaporated under vacuum. A solution of HCl 1N was added dropwise

to the reaction mixture to obtain precipitation of a yellow pale solid, after filtration the solid obtained was dried under vacuum.

M = 17.4g, yield: 98%

^{1}H NMR ($CDCl_3$) : δ 1.3 (s, 9H) ; 4 (s, 3H) ; 6.9 (s, 1H) ; 7.4 (d, 2H) ; 7.5 (d, 2H).



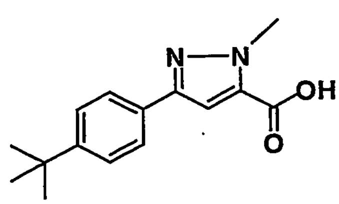
Intermediate 4

Ethyl 3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazole-5-carboxylate.

24,7 mL of Methyl hydrazine was added to a solution of 86g of **Intermediate 1**, in 1 L of EtOH. The reaction mixture was heated at 90°C for 16h, cooled at rt and concentrated under vacuum. 1 L of ethyl acetate was added and the organic layer was washed with brine, (HCl 1N) x2, and brine. The organic layer was dried with Na_2SO_4 after filtration and evaporation, under vacuum, the solid obtained was purified on flash silica column Cyclohexane/AcOEt (95/5) first eluted then Cyclohexane/AcOEt (95/5).

First eluted intermediate 4: 41.3g , yield 47%.

^{1}H NMR ($CDCl_3$) : δ 7.54 (d, 2H) ; 7.24 (d, 2H) ; 6.93 (s, 1H) ; 4,2 (q, 3H) ; 4.05 (s, 3H) ; 1.22 (t, 3H) ; 1.17 (s, 9H).



Intermediate 5

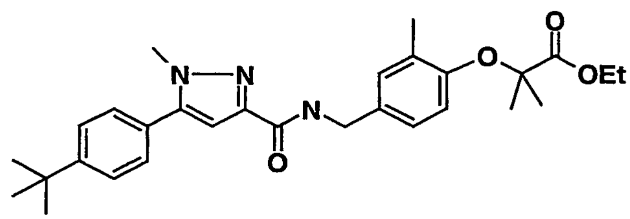
3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazole-5-carboxylic acid.

25 mL of EtOH and 42 ml of NaOH 1N was added to a solution of 4 g of **Intermediate 4**, in 25 mL of THF. The reaction mixture was stirred 2h30 at rt, EtOH and THF were evaporated under vacuum. A solution of HCl 1N was added to the

reaction mixture to obtain precipitation of a white solid. After filtration, the resulting solid was rinsed with water and dried under vacuum.

M = 3.62 g, yield: quantitative.

^{1}H NMR (DMSO-d6) : δ 7.75 (d, 2H) ; 7.43 (d, 2H) ; 7.24 (s, 1H) ; 4.12 (s, 3H); 1.3 (s, 9H)



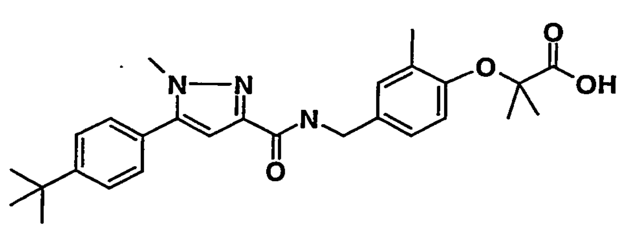
Intermediate 6

Ethyl 2-{4-[({[5-(4-*tert*-butylphenyl)-1-methyl-1*H*-pyrazol-3-yl]carbonyl}amino)methyl]-2-methylphenoxy}-2-methylpropanoate

21mL of $SOCl_2$ was added dropwise under nitrogen atmosphere to a suspension of 14.85 g of **Intermediate 3** in 700 ml of anhydrous toluene. The reaction mixture was heated at 80°C for 3h30. Toluene and $SOCl_2$ were evaporated under vacuum and the residue was diluted in 400 mL of anhydrous CH_2Cl_2 and added dropwise to a solution of 15.56g of **Intermediate 12** 24.3 mL of Et_3N in 800 mL of CH_2Cl_2. The reaction mixture was stirred 2H at rt, then washed twice with HCl 1N, and with brine. The organic layer was dried with Na_2SO_4, after filtration and evaporation of solvent under vacuum the resulting oil was purified by SiO_2 flash chromatography (CH_2Cl_2/AcOEt : 95/5)

M: 32g of yellow oil yield: 96%

^{1}H NMR ($CDCl_3$) : δ 7.4 (d, 2H) ; 7.3 (d, 2H) ; 6.95-7.1 (m, 3H) ; 6.8 (s, 1H) ; 6.5 (d, 1H) ; 4.5 (d, 2H) ; 4.2 (q, 3H) ; 3.8 (s, 3H) ; 2.2 (s, 3H) ; 1.5 (s, 6H) ; 1.3 (s, 9H) ; 1.2 (t, 3H).



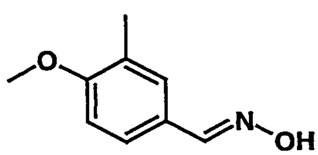
Example 1

2-[(4-{[({5-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-methylphenyl)oxy]-2-methylpropanoic acid

1L of NaOH 1N was added dropwise to a solution of 70 g of **Intermediate 6** in 250 mL of EtOH. The reaction mixture was heated at 90°C for 3 H. EtOH was evaporated under vacuum and 500mL of H_2O was added then HCl 1N until a pH of 1 was obtained. A white precipitate appeared and the mixture was left at rt for 12 h to obtain complete precipitation. The white precipitate was filtered then solubilised in ACOEt and washed with water. The organic layer was dried on Na_2SO_4 filtered and concentrated under vacuum. The white powder obtained was re-crystallised in isopropyl acetate (1g of compound in 5 ml of isopropyl acetate) to afford 53g of white crystals.

Mp: 139°C

^{1}H-NMR ($CDCl_3$) : δ 7.3 (d, 2H) ; 7.1 (m, 3H) ; 7 (s, 1H) ; 6.8 (d, 1H) ; 6.7 (s, 1H) ; 6.6 (d, 1H) ; 4,3 (d, 2H) ; 3,7 (s, 3H) ; 2 (s, 3H) ; 1.4 (s, 6H) 1.1 (s, 9H).

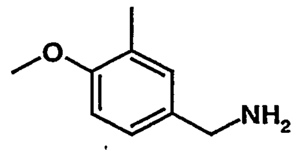


Intermediate 7

3-methyl-4-(methyloxy)benzaldehyde oxime

H_2NOH,HCl (1.6 equiv.), (3equiv.) NaOAc in 150mL H_2O was added to **4-methoxy-3-methylbenzalehyde** (1 equiv., Acros) in EtOH (150mL) at rt and the reaction stirred for 2h. The EtOH was evaporated, and the residue extracted with CH_2Cl_2 (3 x 50mL). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and evaporated to dryness to afford the title compound as a white solid (93%).

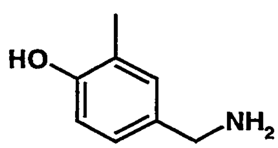
Mp 71-73°C



Intermediate 8

{[3-methyl-4-(methyloxy)phenyl]methyl}amine

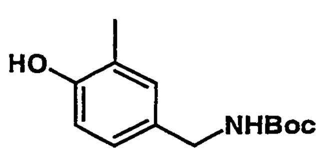
To Intermediate **intermediate 7** (1 equiv.) in MeOH (200mL) at rt was added [$MeCO_2$]NH_4 (6 equiv.), Pd/C (0.01 equiv.) and molecular sieves The reaction was then heated to reflux for 18h. The reaction mix was filtered through celite, evaporated to dryness and treated with HCl (1N). The aqueous layer was washed with CH_2Cl_2 , filtered, basified to pH >14 and extracted with CH_2Cl_2 (3 x 50mL). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and evaporated to dryness to afford the title compound as an oil (46%).
MS m/z 151



Intermediate 9

4-(aminomethyl)-2-methylphenol

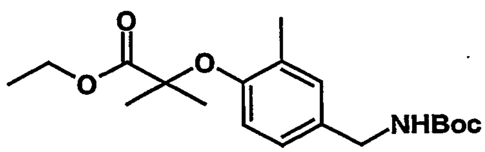
Intermediate 8 (1 equiv.) in excess 40% HBr/H_2O (Aldrich) was refluxed for 18h. The reaction was then evaporated to dryness to afford the title compound hydrobromide salt as a grey solid (97%).
Mp 235-237°C



Intermediate 10

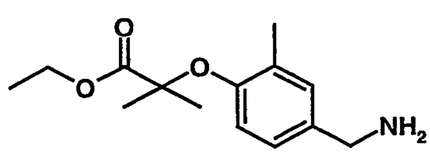
1,1-dimethylethyl [(4-hydroxy-3-methylphenyl)methyl]carbamate

Et_3N (3 equiv.), Boc anhydride (0.95 equiv.) in CH_2Cl_2 (50mL) were added dropwise to **Intermediate 9** (1 equiv.) in CH_2Cl_2 (300mL) at 0°C. The reaction was allowed to warm to rt and stirring continued for 18h. HCl (1N) was added and the reaction extracted with CH_2Cl_2 (3 x 100mL). The organic layers washed with H_2O, dried over Na_2SO_4, filtered and the solvent removed under vacuum to afford the title compound as a white solid (96%).
Mp 105-107°C



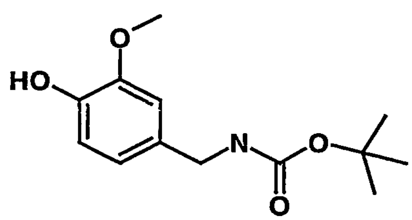
Intermediate 11
Ethyl 2-({4-[({[(1,1-dimethylethyl)oxy]carbonyl}amino)methyl]-2-methylphenyl}oxy)-2-methylpropanoate

K_2CO_3 (3 equiv.) was added to **Intermediate 10** (1 equiv.) in DMF (150mL) and the reaction heated to 70°C. **Ethyl 2-bromo-2-methylproprionate** (1.3 equiv.) was added droppwise and the reaction was stirred for 72h at 70°C. The reaction was poured onto ice and extracted with CH_2Cl_2 (3 x 150mL). The combined organic layers were washed with NaOH (0.5N), then H_2O and dried over Na_2SO_4. The solution filtered, evaporated to dryness to afford the title compound as an oil (69%).
^1H NMR ($CDCl_3$) : δ 7.05 (d, 1H), 6.90 (dd, 1H), 6.60 (d, 1H), 4.80 (bs, 1H), 4.25 (q, 2H), 4.20 (d, 2H), 2.20 (s, 3H), 1.60 (s, 6H), 1.45 (s, 9H), 1.25 (t, 3H).



Intermediate 12
Ethyl 2-{[4-(aminomethyl)-2-methylphenyl]oxy}-2-methylpropanoate

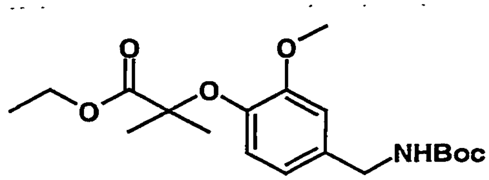
CF_3COOH (7 equiv.) was added dropwise to **Intermediate 11** (1 equiv.) in CH_2Cl_2 (10mL) at rt and the reaction stirred at rt for 18h. The reaction was evaporated to dryness, treated with a saturated K_2CO_3 solution and extracted with CH_2Cl_2 (3 x 150mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness to afford the title compound as an oil (62%).
^1H NMR ($CDCl_3$) : □ 7.00 (d, 1H), 6.90 (dd, 1H), 6.55 (d, 1H), 4.20 (q, 2H), 3.70 (s, 2H), 2.15 (s, 3H), 1.85 (bs, 2H), 1.50 (s, 6H), 1.20 (t, 3H).



Intermediate 13

1,1-dimethylethyl {[4-hydroxy-3(methyloxy) phenyl]methyl} carbamate

Et_3N (3 equiv.). Boc anhydride (0.95 equiv.) in CH_2Cl_2 (50mL) was added to **(4-hydroxy-3-methoxybenzylamine hydrochloride)** (1 equiv., Aldrich) in CH_2Cl_2 (300mL) at 0°C. The reaction was allowed to warm to rt and stirring continued for 18h. The reaction was then poured into NaOH (1N) and the mixture extracted with NaOH (3 x 50mL). The aqueous phases combined, acidified with HCl (1N) and extracted with CH_2Cl_2 (3 x 100mL). The oranic layers washed with H_2O, dried over Na_2SO_4, filtered and the solvent removed under vaccum to afford the title compound as a clear oil (97%).
^1H NMR ($CDCl_3$); δ 6.75 (m, 3H), 5.55 (bs, 1H), 4.75 (bs, 1H), 4.15 (d, 2H), 3.80 (s, 3H), 1.40 (s, 9H).

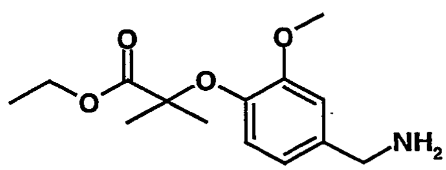


Intermediate 14

Ethyl 2-{[4-[({[(1,1-dimethylethyl)oxy]carbonyl}amino)methyl]-2-(methyloxy)phenyl]oxy}-2-methylpropanoate

K_2CO_3 (3 equiv.) and **ethyl 2-bromo-2-methylproprionate** (1.3 equiv.). was added to **Intermediate 13** (1 equiv.) in DMSO (100mL). The reaction was stirred while heating at 100°C for 3h. The reaction was poured onto ice and extracted with CH_2Cl_2 (3 x 150mL). The combined organic layers were washed with NaOH (1N), then H_2O and dried over Na_2SO_4. The solution filtered, evaporated to dryness and the crude product cristallized from hot hexane to afford the title compound as a brown solid (63%).

Mp 107-109°C

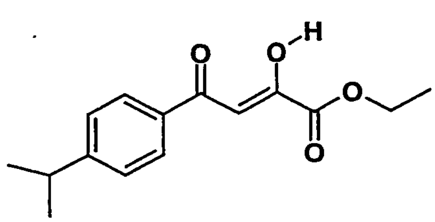


Intermediate 15

Ethyl 2-{[4-(aminomethyl)-2-(methyloxy)phenyl]oxy}-2-methylpropanoate

CF_3COOH (7 equiv.) was added dropwise to **Intermediate 14** (1 equiv.) in CH_2Cl_2 (10mL) at rt and the reaction stirred at rt for 18h. The reaction was evaporated to dryness, treated with a saturated K_2CO_3 solution and extracted with CH_2Cl_2 (3 x 150mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness to afford the title compound as an oil (100%).

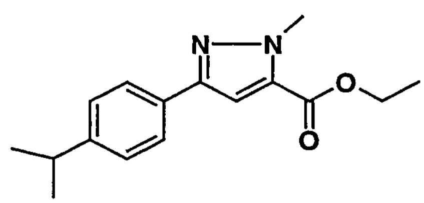
MS m/z 267



Intermediate 16

Ethyl 4-[4-(1-methylethyl)phenyl]-2,4-dioxobutanoate

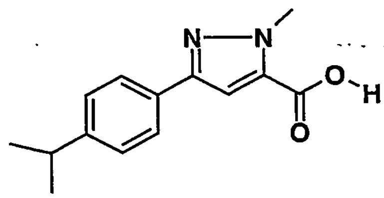
3.4 g of Na is added portionwise to 350 mL of EtOH in a 3L neck flask under nitrogen atmosphere at 0°C. A solution of 8.4g of p-iso-propylacetophenone in 50 ml of EtOH was added dropwise and the reaction mixture was stirred for 20 min at 0°C then, 21.6 g of ethyl oxalate in 50 mL of EtOH was added dropwise. The reaction mixture was for 2h at 80°C. The reaction mixture was cooled to rt and concentrated under vacuum. 500 mL of Ethyl acetate were added and the organic layer was successively washed with brine, HCl (1N) x2, and brine.
The organic layer was dried with Na_2SO_4, after filtration and evaporation under vacuum, the resulting red oil was purified using preparative chromatography providing the title compound as an oil.
Yield: 18%
^{1}H NMR ($CDCl_3$): δ 7.86 (d,1H) ; 7.28 (d, 2H) ; 6.99 (s, 1H) ; 4.33 (q , 3H) ; 2.91 (hept, 1H) ; 1.34 (t, 3H) ; 1.21 (d, 1H).



Intermediate 17
Ethyl 1-methyl-3-[4-(1-methylethyl)phenyl]-1*H*-pyrazole-5-carboxylate

1.65 mL of Methyl hydrazine was added to a solution of 5.4g of **Intermediate 16** in 200 mL of EtOH. The reaction mixture was heated at 90°C for 24h, cooled at rt and three quarters of the ethanol was removed under vacuum. The solution was diluted with ethyl acetate and was washed with HCl 1N, and brine. The organic layer was dried over sodium sulfate and evaporated to dryness. The resulting solid was purified on flash silica column using Cyclohexane/AcOEt (90/10) then Cyclohexane/AcOEt (80/20).
The title compound was identified as the less polar isomer and recrystallized from butan-1-01 at 0°C to give the title compound as 2.05 g of colourless crystals
Yield: 36%

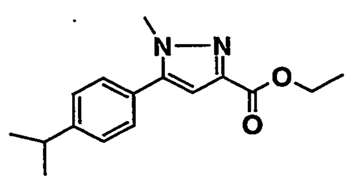
^{1}H NMR ($CDCl_3$) : δ 7.70 (d, 2H) ; 7.28 (d, 2H) ; 7.11 (s, 1H) ; 4,39 (q, 3H) ; 4.24 (s, 3H) ; 2.95 (hept, 1H) ; 1.43 (t, 3H) ; 1.29 (d, 6H).



Intermediate 18

1-methyl-3-[4-(1-methylethyl)phenyl]-1*H*-pyrazole-5-carboxylic acid.

20 ml of EtOH and 38 ml of NaOH 1N were added to a solution of 1 g of **Intermediate 17** in 20 ml of THF. The reaction mixture was stirred 1h at rt, EtOH and THF were evaporated under vacuum. A solution of HCl 1N was added to the reaction mixture to obtain precipitation of a white solid. After filtration, the resulting white solid was rinsed with water and dried under vacuum (M =0.71 g).
Yield: 79%
^{1}H NMR ($CDCl_3$) : δ 7.65 (d, 2H) ; 7.20 (d, 2H) ; 7.15 (s, 1H) ; 4.17 (s, 3H) ; 2.86 (hept, 1H) ; 1.20 (d, 6H).

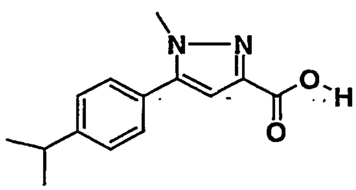


Intermediate 19

Ethyl 1-methyl-5-[4-(1-methylethyl)phenyl]-1*H*-pyrazole-3-carboxylate

1.65 mL of Methyl hydrazine was added to a solution of 5.4g of **Intermediate 16** in 200 mL of EtOH. The reaction mixture was heated at 90°C for 24h, cooled at rt and three quarters of the ethanol was removed under vacuum. The solution was diluted with ethyl acetate and was washed with HCl 1N, and brine. The organic layer was dried over sodium sulfate and evaporated to dryness. The resulting solid was

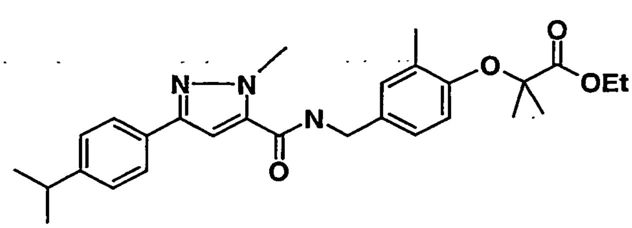
purified on flash silica column using Cyclohexane/AcOEt (90/10) then Cyclohexane/AcOEt (80/20).
The title compound was eluted as the more polar isomer and recrystallized from petroleum ether to give the title compound as 1 g of colourless crystals
Yield: 18%
^{1}H NMR ($CDCl_3$) : δ 7.15 (m, 4H) ; 6.65 (s, 1H) ; 4,25 (q, 3H) ; 3.77 (s, 3H) ; 2.79 (hept, 1H) ; 1.23 (t, 3H) ; 1.11 (d, 6H).



Intermediate 20

1-methyl-5-[4-(1-methylethyl)phenyl]-1*H*-pyrazole-3-carboxylic acid

To a solution of 260 mg of **Intermediate 19** in 1 mL of THF and 3 mL of EtOH was added 6 mL of NaOH 1N. The reaction mixture was stirred 1h30 at rt, EtOH and THF were evaporated under vacuum. Precipitation of the carboxylic acid was achieved by acidifying with a 1N solution of HCl. After filtration, the resulting beige powder was rinsed with water and dried under vacuum (M =219 mg).
Yield: 94%
^{1}H NMR (DMSO d6) : δ 7.48 (d, 2H) ; 7.38 (d, 2H) ; 6.79 (s, 1H) ; 3.90 (s, 3H) ; 2.96 (hept, 1H) ; 1.24 (d, 6H).

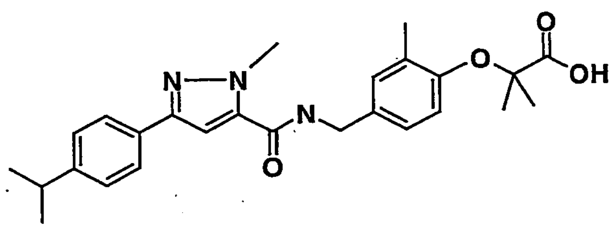


Intermediate 21
Ethyl 2-methyl-2-[(2-methyl-4-{[({1-methyl-3-[4-(1-methylethyl) phenyl]-1*H*-pyrazol-5-yl} carbonyl) amino]methyl} phenyl)oxy] propanoate

Intermediate 18 (134 mg, 0.55 mmol) was dissolved in the minimum amount of DMF (about 5 mL), HOBT (74 mg, 0.55 mmol), EDCI (105 mg, 0.55 mmol), Et_3N (155 µL, 1.1 mmol) and **intermediate 12** (144 mg, 0.5 mmol) were successively added. The mixture was stirred at rt for 26 hours and the DMF was evaporated under reduced pressure. The residue was diluted in EtAOc and washed with a sat. $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The product was then purified by flash chromatography on silica gel (CH_2CL_2/AcOEt = 95/5) to afford the title compound as white crystals

Yield: 77%

^{1}H NMR ($CDCl_3$) : δ 7.60 (d, 2H) ; 7.17 (d, 2H) ; 7.06 (m, 1H) ; 6.94 (dd, 1H) ; 6.65 (s, 1H) ; 6.56 (d, 1H) ; 6.16 (t, 1H) ; 4.43 (d, 2H) ;4.18 (q, 2H) ; 4.17 (s, 3H) ; 2.85 (hept, 1H) ; 2.17 (s, 3H) ; 1.53 (s, 6H) ; 1.20 (t, 3H) ; 1.19 (d, 6H).



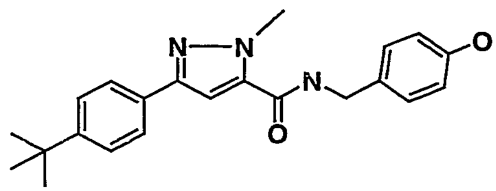
Example 2

2-methyl-2-[(2-methyl-4-{[({1-methyl-3-[4-(1-methylethyl)phenyl]-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}phenyl)oxy]propanoic acid.

Intermediate 21, (178 mg, 0.373 mmol) was dissolved in 50 mL of THF and 1N NaOH (3.7 mL, 3.73 mmol) was added. The solution was heated at 80°C for 1 hour and the solvents were evaporated under reduced pressure. The resulting pale yellow product was dissolved in water and acidified with 1N HCl. The white precipitate was filtered off, washed with water and dried under vacuum to give the title compound as 136 mg of a white powder.

Yield = 81%

^{1}H NMR ($CDCl_3$) : δ 7.60 (d, 2H) ; 7.17 (d, 2H) ; 7.09 (m, 1H) ; 7.00 (dd, 1H) ; 6.74 (d, 1H) ; 6.66 (s, 1H) ; 6.25 (t, 1H) ; 4.43 (d, 2H) ; 4.16 (s, 3H) ; 2.85 (hept, 1H) ; 2.18 (s, 3H) ; 1.56 (s, 6H) ; 1.19 (d, 6H).



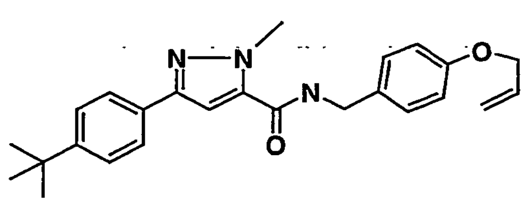
Intermediate 22

3-[4-(1,1-dimethylethyl)phenyl]-*N*-[(4-hydroxyphenyl)methyl]-1-methyl-1*H*-pyrazole-5-carboxamide

21 mL of $SOCl_2$ was added dropwise to a suspension of **Intermediate 5**, (500 mg, 1.9 mmol) in 100 ml of anhydrous toluene and the reaction mixture was heated at 90°C for 2hours. Toluene and $SOCl_2$ were evaporated under vacuum and the residue was diluted in 50 ml of anhydrous CH_2Cl_2 and added dropwise to a solution of **p-hydroxybenzylamine hydrobromide** (887 mg, 4.3 mmol) in 1.35 mL of Et_3N (2.5 eq.), 50 mL of CH_2Cl_2 and 5 mL DMF (required amount to get solubility). The reaction mixture was stirred 18 hours at rt, evaporated to dryness and suspended in 1N HCl. The precipitate was filtered off, diluted in 50 mL of EtOH and heated with 1N NaOH (10 mL) at 80°C for 1 hour to get rid of the phenol ester. The solvents were removed in vacuum and the phenol was precipitated using a sat. NH_4Cl solution, washed with water and dried under reduced pressure to afford the title compound as a beige powder (530 mg)

Yield: 74%

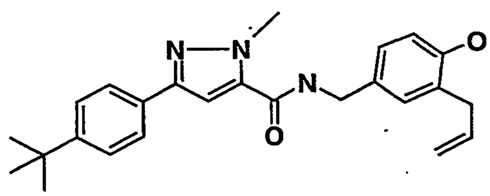
^{1}H NMR (DMSO d6) : δ 8.99 (m, 1H) ; 7.66 (d, 2H) ; 7.44 (d, 2H) ; 7.26 (s, 1H); 7.13 (d, 2H) ; 6.73 (d, 2H) ; 4.33 (d, 2H) ; 4.10 (s, 3H); 1.29 (s, 9H).



Intermediate 23

3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-*N*-{[4-(2-propen-1-yloxy)phenyl]methyl}-1*H*-pyrazole-5-carboxamide

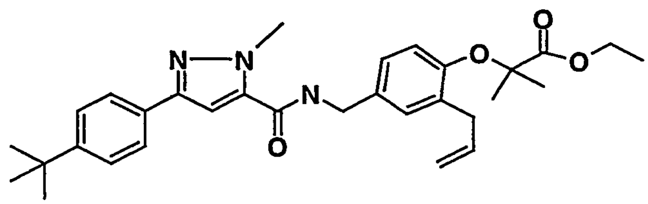
Intermediate 22 (530 mg, 1.4 mmol) was dissolved in 50 mL of acetone, K_2CO_3 (300 mg, 1.8 mmol) was added followed by addition of **allyl bromide** (200 µl, 1.4 mmol) and the resulting mixture was stirred at 70°C for 18 hours. At this stage, 3 more eq. of K_2CO_3 and 2 eq. of **allyl bromide** were added and the reaction mixture was heated for an additional 18 hours to completion. Solvents were evaporated and the residue was dissolved in ether (50 mL) and washed with water (50 mL). The organic layer was dried over sodium sulfate and evaporated to dryness to provide the title compound as a beige powder (580 mg).
Yield : 99%
^{1}H NMR ($CDCl_3$) : δ 6.61 (d, 2H) ; 7.34 (d, 2H) ; 7.21 (d, 2H) ; 6.85 (d, 2H) ; 6.65 (s, 1H) ; 6.19 (t, 1H) ; 5.98 (m, 1H) ; 5.32 (dd, 2H) ; 5.22 (dd, 2H); 4.47 (m, 4H) ; 4.17 (s, 3H) ; 1.26 (s, 9H).



Intermediate 24

3-[4-(1,1-dimethylethyl)phenyl]-*N*-{[4-hydroxy-3-(2-propen-1-yl)phenyl]methyl}-1-methyl-1*H*-pyrazole-5-carboxamide.

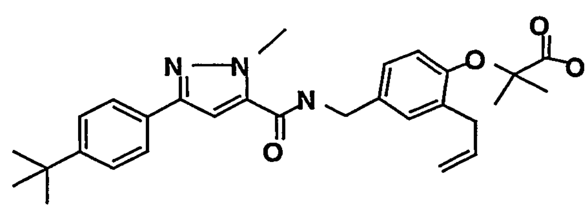
Intermediate 23 (580 mg, 1.39 mmol) was heated neat at 250°C in a sealed tube for 30 minutes. After cooling down, the phenol was isolated without further purification as a beige powder (300 mg).
Yield : 52%
^{1}H NMR (DMSO d6) δ 9.30 (s, 1H) ; 8.96 (t, 1H) ; 7.67 (d, 2H) ; 7.44 (d, 2H) ; 7.24 (m, 1H) ; 7.00 (m, 2H) ; 6.75 (d, 1H) ; 5.92 (m, 1H) ; 5.01 (m, 2H) ; 4.31 (d, 2H); 4.09 (s, 3H) ; 3.30 (m, 2H) ; 1.29 (s, 9H).



Intermediate 25

Ethyl 2-{[4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-(2-propen-1-yl)phenyl]oxy}-2-methylpropanoate.

Intermediate 24 (300 mg, 0.72 mmol) was dissolved in 50 mL of acetone with **ethyl 2-bromoisobutyrate** (300 µL, 2.1 mmol) and K_2CO_3 (287 mg, 2.1 mmol) and the reaction mixture was heated at 70°C for 72 hours. After evaporation of the solvents, the residue was diluted in ether and washed with water. The organic layer was dried over sodium sulfate and evaporated to dryness and then purified by flash chromatography on silica gel (CH_2CL_2/MeOH = 99.5/0.5 to 98/2) to afford the title compound as a white powder recrystallized from diisopropyl oxide (220 mg).
Yield: 58%
^{1}H NMR (DMSO d6) : δ 9.01 (t, 1H) ; 7.67 (d, 2H) ; 7.44 (d, 2H) ; 7.26 (s, 1H) ; 7.10 (m, 2H) ; 6.58 (d, 1H) ; 5.05 (m, 2H) ; 4.35 (m, 2H); 4.17 (q, 2H) ; 4.09 (s, 3H) ; 3.30 (m, 2H) ; 1.51 (s, 6H) ; 1.29 (s, 9H) ; 1.17 (q, 3H).

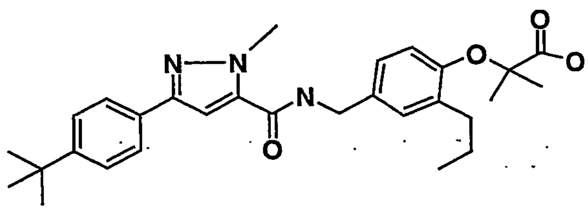


Example 3

2-{[4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-(2-propen-1-yl)phenyl]oxy}-2-methylpropanoic acid.

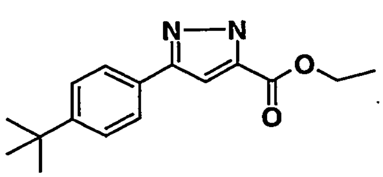
Intermediate 25 (220 mg, 0.41 mmol) was dissolved in 50 mL of ethanol and 2 mL of 1N NaOH (2 mmol) and the solution was heated at 80°C for 18 hours.

Concentration in vacuum followed by acidification with 1N HCl and filtration of the precipitate give 90 mg of a white powder.
Yield : 45%
^{1}H NMR ($CDCl_3$) : δ 7.47 (d, 2H) ; 7.24 (d, 2H) ; 7.08 (s, 1H) ; 6.94 (m, 2H) ; 6.57 (m, 2H) ; 6.13 (m, 1H) ; 5.79 (m, 1H) ; 4.92 (m, 2H) ; 4.35 (m, 2H) ; 4.04 (s, 3H) ; 3.23 (d, 2H) ; 1.46 (s, 6H) ; 1.15 (s, 9H).



Example 4
2-[(4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-propylphenyl)oxy]-2-methylpropanoic acid.

Example 3 (90mg, 0.18 mmol), ammonium formate (120 mg, 1.9 mmol) and Pd/C10% (50mg) were stirred in 50 mL of ethanol for 2 hours at rt, then for 18 hours at 60°C. The reaction mixture was filtered through a celite pad and the resulting product was purified by preparative HPLC (Xterra MS C18 19x50 mm, 5μm, H_2O/CH_3CN = 80/20 to 20/80 in 10 minutes) to afford the title compound as a pale pink powder.
Yield : 22%
^{1}H NMR ($CDCl_3$) : δ 7.57 (d, 2H) ; 7.31 (d, 2H) ; 7.04 (s, 1H) ; 6.92 (m, 1H) ; 6.66 (m, 2H) ; 6.45 (m, 1H) ; 4.41 (d, 2H) ; 4.13 (s, 3H) ; 4.49 (t, 2H) ; 1.53 (s, 6H); 1.24 (s, 9H) ; 1.20 (m, 2H) ; 0.87 (t, 3H).

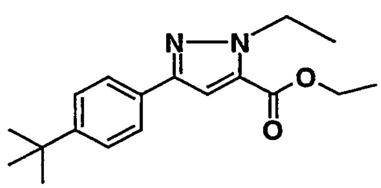


Intermediate 26
Ethyl 3-[4-(1,1-dimethylethyl)phenyl]-1*H*-pyrazole-5-carboxylate

Hydrazine hydrate (13.4 mL, 0.276 mol) was added to a solution of **intermediate 1** (76.2 g, 0.276 mol) in 750 mL of ethanol under a nitrogen atmosphere and the mixture was heated at 90°C for 3 hours. The yellow crystals were separated by filtered and the red filtrate was cooled down promoting the formation of a second crop of yellow crystals which were filtrated too. Ethanol was evaporated and the residue was diluted in the minimum amount of CH_2CL_2 promoting precipitation of a white solid filtered off and rinsed with CH_2CL_2 affording the title compound as a white powder (37.8 g).

Yield : 50%

[1]H NMR (DMSO d6) : δ 7.76 (d, 2H) ; 7.46 (d, 2H) ; 7.18 (brs, 1H) ; 4,31 (q, 2H) ; 1.32 (t, 3H) ; 1.30 (s, 9H).



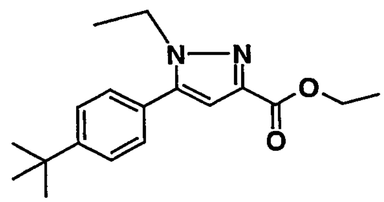
Intermediate 27

Ethyl 3-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazole-5-carboxylate.

K_2CO_3 (28.7 g, 207 mmol) and ethyl iodide (27.9 mL, 346 mmol) was added to a solution of **intermediate 26** (18.8 g, 69 mmol) in 500 mL of acetone. The reaction mixture was heated at 70 °C for 19h30 under a nitrogen atmosphere and after cooling down, the inorganic salts were filtered and the filtrate was evaporated to dryness. The resulting solid was diluted in EtOAc and water and the organic layer was separated and washed with 1N HCl and then with brine. The organic layer was dried over sodium sulfate and evaporated to dryness and then purified by flash chromatography on silica gel (cyclohexane/EtOAc = 90/10 to 80/20) to afford the title compound as a yellow oil which crystallizes on standing (14.4 g). The other N-Et isomer was also purified (5.4 g, 26% yield).

Yield : 70%

[1]H NMR ($CDCl_3$) : δ 7.55 (d, 2H) ; 7.23 (d, 2H) ; 6.91 (s, 1H) ; 4,45 (q, 2H) ; 4,16 (q, 2H) ; 1.28 (t, 3H) ; 1.20 (t, 3H) ; 1.15 (s, 9H).



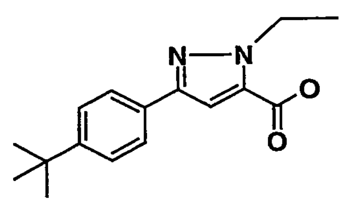
Intermediate 28

Ethyl 5-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazole-3-carboxylate.

K_2CO_3 (28.7 g, 207 mmol) and ethyl iodide (27.9 mL, 346 mmol) was added to a solution of **intermediate 26** (18.8 g, 69 mmol) in 500 mL of acetone. The reaction mixture was heated at 70 °C for 19h30 under a nitrogen atmosphere and after cooling down, the inorganic salts were filtered and the filtrate was evaporated to dryness. The resulting solid was diluted in EtOAc and water and the organic layer was separated and washed with 1N HCl and then with brine. The organic layer was dried over sodium sulfate and evaporated to dryness and then purified by flash chromatography on silica gel (cyclohexane/EtOAc = 90/10 to 80/20) to afford the title compound as a yellow oil (5.4 g).

Yield: 26%

^{1}H NMR ($CDCl_3$) : δ 7.46 (d, 2H) ; 7.30 (d, 2H) ; 6.77 (s, 1H) ; 4,41 (q, 2H) ; 4,23 (q, 2H) ; 1.41 (t, 3H) ; 1.39 (t, 3H) ; 1.34 (s, 9H).



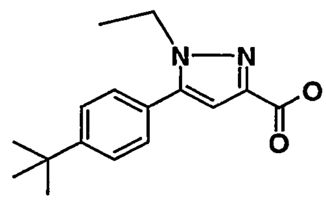
Intermediate 29

3-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazole-5-carboxylic acid.

Intermediate 27 (8.5 g, 28.3 mmol) was dissolved in a minimum amount of THF and 250 mL of ethanol and 283 mL of 1N NaOH (283 mmol) were added. The solution was heated to 80°C for 1 hour and concentrated under vacuum. The resulting white solid was acidified by 1N HCl and the white precipitate was filtered off and dried to provide the title carboxylic acid as 6.7 g of a white powder.

Yield : 87%

^{1}H NMR ($CDCl_3$) : δ 7.54 (d, 2H) ; 7.43 (d, 2H) ; 7.23 (s, 1H) ; 4,66 (q, 2H) ; 1.50 (t, 3H) ; 1.34 (s, 9H).



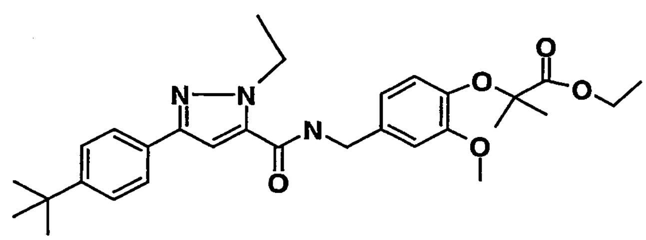
Intermediate 30

5-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazole-3-carboxylic acid.

Intermediate 28 was saponified following the procedure to make 3-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazole-5-carboxylic acid (intermediate 2) providing the title compound as a white powder.

Yield : 71%

^{1}H NMR ($CDCl_3$) : δ 7.48 (d, 2H) ; 7.32 (d, 2H) ; 6.84 (s, 1H) ; 4,25 (q, 2H) ; 1.45 (t, 3H) ; 1.35 (s, 9H).



Intermediate 31

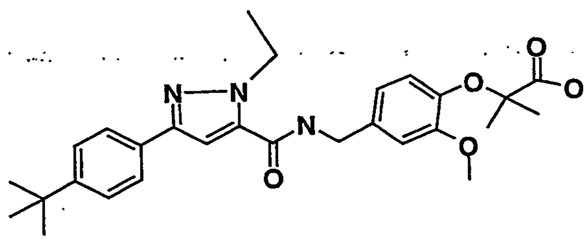
Ethyl 2-{[4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}-2-methylpropanoate.

Intermediate 29 (197 mg, 0.72 mmol) was dissolved in a minimum amount of DMF (about 5 mL), HOBT (98 mg, 0.72 mmol), EDCI (138 mg, 0.72 mmol), Et_3N (203 µL, 1.45 mmol) and **Intermediate 15** (200 mg, 0.66 mmol) were successively added. The mixture was stirred at rt for 26 hours and the DMF was evaporated under reduced pressure. The residue was diluted in EtAOc and washed with 1N HCl (1x),

with a sat. $NaHCO_3$ solution (3x) and with brine (1x), dried over Na_2SO_4, filtered and evaporated to dryness. The product was then purified by flash chromatography on silica gel (CH_2CL_2/AcOEt = 97/3) to afford the title compound as a yellow oil (195 mg).

Yield: 57%

^{1}H NMR ($CDCl_3$) : δ 7.69 (d, 2H) ; 7.41 (d, 2H) ; 6.83 (m, 3H) ; 6.72 (s, 1H) ; 6.30 (t, 1H) ; 4.65 (q, 2H) ; 4.54 (d, 2H) ; 4.23 (q, 2H) ; 3.81 (s, 3H) ; 1.56 (s, 6H) ; 1.49 (t, 3H) ; 1.32 (s, 9H) ; 1.27 (t, 3H).



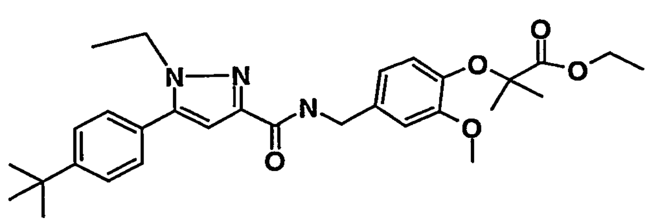
Example 5

2-{[4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}-2-methylpropanoic acid.

Intermediate 31 (190 mg, 0.36 mmol) was dissolved in a minimum amount of THF and 3 mL of ethanol and 3.6 mL of 1N NaOH (3.6 mmol) were added. The solution was heated to 80°C for 1 hour and concentrated under vacuum. The residue was diluted in water and acidified by 1N HCl and the white precipitate was filtered off and dried to provide the title carboxylic acid as 151 mg of a white powder.

Yield : 85%

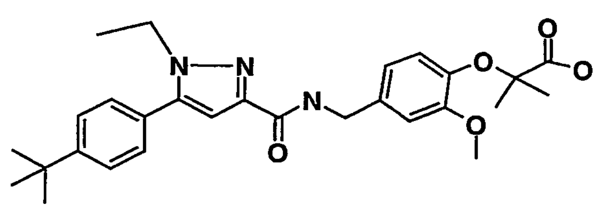
^{1}H NMR ($CDCl_3$) : δ 7.69 (d, 2H) ; 7.41 (d, 2H) ; 6.99 (d, 1H) ; 6.94 (s, 1H) ; 6.90 (d, 1H) ; 6.74 (s, 1H) ; 6.37 (t, 1H) ; 4.65 (q, 2H) ;4.58 (d, 2H) ; 3.89 (s, 3H) ; 1.51 (s, 6H) ; 1.49 (t, 3H) ; 1.32 (s, 9H).



Intermediate 32

Ethyl 2-{[4-{[({5-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}-2-methylpropanoate.

Intermediate 30 (197 mg, 0.72 mmol) was dissolved in a minimum amount of DMF (about 5 mL), HOBT (98 mg, 0.72 mmol), EDCI (138 mg, 0.72 mmol), Et_3N (203 µL, 1.45 mmol) and **Intermediate 15** (200 mg, 0.66 mmol) were successively added. The mixture was stirred at rt for 26 hours and the DMF was evaporated under reduced pressure. The residue was diluted in EtAOc and washed with 1N HCl (2x), with a sat. $NaHCO_3$ solution (3x) and with brine (2x), dried over Na_2SO_4, filtered and evaporated to dryness. The product was then purified by flash chromatography on silica gel (CH_2CL_2/AcOEt = 97/3) to afford the title compound as a white oil (257 mg).
Yield : 75%
^{1}H NMR ($CDCl_3$) : δ 7.47 (d, 2H) ; 7.31 (d, 2H) ; 7.20 (t, 1H) ; 6.89 (s, 1H) ; 6.81 (brs, 3H) ; 4.56 (d, 2H) ; 4.23 (q, 2H) ; 4.13 (q, 2H) ; 3.80 (s, 3H) ; 1.55 (s, 6H) ; 1.41 (t, 3H) ; 1.35 (s, 9H) ; 1.27 (t, 3H).

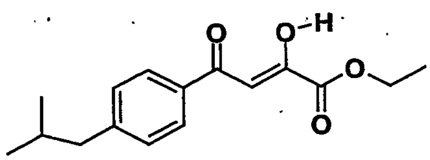


Example 6

2-{[4-{[({5-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}-2-methylpropanoic acid.

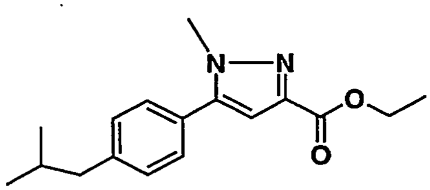
Intermediate 32 (257 mg, 0.49 mmol) was dissolved in a minimum amount of THF and 4 mL of ethanol and 4.9 mL of 1N NaOH (4.9 mmol) were added. The solution was stirred at rt for 2 hour and concentrated under vacuum. The residue was diluted in water and acidified by 1N HCl and the white precipitate was filtered off and dried to provide the title carboxylic acid as 205 mg of a white powder.
Yield : 85%

^1H NMR ($CDCl_3$) : δ 7.47 (d, 2H) ; 7.30 (d, 2H) ; 7.26 (m, 1H) ; 6.95 (m, 3H) ; 6.81 (s, 1H) ; 4.60 (d, 2H) ; 4.14 (q, 2H) ; 3.89 (s, 3H) ; 1.50 (s, 6H) ; 1.41 (t, 3H) ; 1.35 (s, 9H).



Intermediate 33
Ethyl 4-[4-(2-methylpropyl)phenyl]-2,4-dioxobutanoate.

Sodium (2.53 g, 0.11 mol) was added portionwise at 0°C in 200 mL of anhydrous ethanol under a nitrogen atmosphere. After dissolution was completed, a solution of **4'-isobutylacetophenone** (17.6 g, 0.1 mol) in 30 mL of anhydrous ethanol was added dropwise at 0°C. When the addition was over, the mixture was stirred at 0°C for 30 minutes and a solution of **ethyloxalate** (16.06 g, 0.11 mol) in 25 mL of anhydrous ethanol was added dropwise. The mixture was stirred at rt for 16 hours and evaporated under reduced pressure. The oily product was dissolved in AcOEt and washed with 1N HCl (2x), with brine (1x), dried over Na_2SO_4, filtered and evaporated to dryness giving the title compound as an orange oil (28 g). The crude product was used without further purification (8% of starting material is remaining).
Yield : quant.
^1H NMR ($CDCl_3$): δ 15.31 (brs, 1H) ; 7.84 (d, 2H) ; 7.20 (d, 2H) ; 6.99 (s, 1H) ; 4.32 (q, 2H) ; 2.49 (m, 2H) ; 1.84 (m, 1H) ; 1.33 (t, 3H) ; 0.84 (d, 6H).

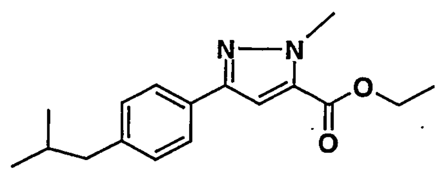


Intermediate 34
Ethyl 1-methyl-5-[4-(2-methylpropyl)phenyl]-1*H*-pyrazole-3-carboxylate.

5.7 mL of methyl hydrazine was added to a solution of **Intermediate 33** (10 g, 36 mmol) in 300 mL of EtOH was added and the reaction mixture was heated to reflux for 24 hours, cooled at rt and concentrated to a volume of approximately 70 mL. The mixture was diluted with EtOAc, washed with 1N HCl and with brine. The organic layer was dried with Na_2SO_4, filtrated and evaporated under vacuum and the resulting red oil was chromatographied on silica gel (Cyclohexane/AcOEt = 90/10 to 80/20). The title compound was eluted as the more polar isomer (yellow oily product, 2.25 g)

Yield : 22%

^{1}H NMR ($CDCl_3$) : δ 7.30 (d, 2H) ; 7.23 (d, 2H) ; 6.82 (s, 1H) ; 4,41 (q, 2H) ; 3.94 (s, 3H) ; 2.52 (d, 2H) ; 1.90 (hept, 1H) ; 1.40 (t, 3H) ; 0.92 (s, 6H).



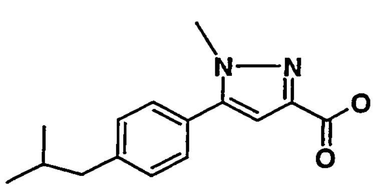
Intermediate 35

Ethyl 1-methyl-3-[4-(2-methylpropyl)phenyl]-1*H*-pyrazole-5-carboxylate.

5.7 mL of methyl hydrazine was added to a solution of **Intermediate 33** (10 g, 36 mmol) in 300 mL of EtOH was added and the reaction mixture was heated to reflux for 24 hours, cooled at rt and concentrated to a volume of approximately 70 mL. The mixture was diluted with EtOAc, washed with 1N HCl and with brine. The organic layer was dried with Na_2SO_4, filtered and evaporated under vacuum and the resulting red oil was chromatographied on silica gel (Cyclohexane/AcOEt = 90/10 to 80/20). The title compound was eluted as the less polar isomer (yellow oily product, 5.79 g)

Yield : 56%

^{1}H NMR ($CDCl_3$) : δ 7.68 (d, 2H) ; 7.17 (d, 2H) ; 7.09 (s, 1H) ; 4,36 (q, 2H) ; 4.21 (s, 3H) ; 2.49 (d, 2H) ; 1.87 (hept, 1H) ; 1.39 (t, 3H) ; 0.90 (s, 6H).



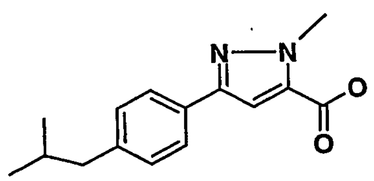
Intermediate 36

1-methyl-5-[4-(2-methylpropyl)phenyl]-1*H*-pyrazole-3-carboxylic acid.

Intermediate 34 (1.1 g, 3.85 mmol) was dissolved in 25 mL of THF and 25 mL of ethanol and 7.7 mL of 1N NaOH (7.7 mmol) were added. The solution was stirred at rt for 3 hours and concentrated under vacuum. The residue was diluted in 10 mL of water and acidified with 1N HCl and the gummy product was filtered off, triturated with pentane and dried to provide the title carboxylic acid as 980 mg of a beige powder.

Yield : quantitative

^{1}H NMR ($CDCl_3$) : δ 7.22 (d, 2H) ; 7.14 (d, 2H) ; 6.70 (s, 1H) ; 3.83 (s, 3H) ; 2.42 (d, 2H) ; 1.80 (hept, 1H) ; 0.92 (s, 6H).



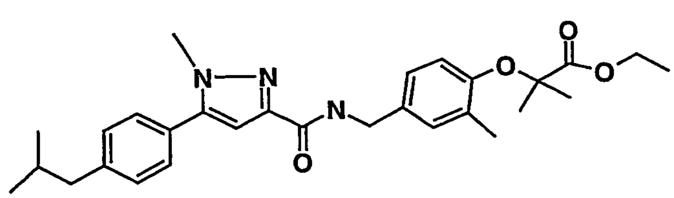
Intermediate 37

1-methyl-3-[4-(2-methylpropyl)phenyl]-1*H*-pyrazole-5-carboxylic acid.

Following the procedure to make **Intermediate 36** , the title compound was isolated as a beige powder.

Yield : 93%

^{1}H NMR ($CDCl_3$) : δ 7.70 (d, 2H) ; 7.22 (s, 1H) ; 7.19 (d, 2H) ; 4.24 (s, 3H) ; 2.49 (d, 2H) ; 1.88 (hept, 1H) ; 0.91 (s, 6H).



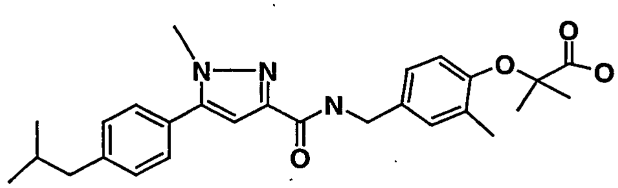
Intermediate 38

Ethyl 2-methyl-2-[(2-methyl-4-{[({1-methyl-5-[4-(2-methylpropyl) phenyl]-1*H*-pyrazol-3-yl} carbonyl) amino] methyl} phenyl) oxy] propanoate

Intermediate 36 (142 mg, 0.55 mmol) was dissolved in 3 mL of DMF, HOBT (75 mg, 0.55 mmol), EDCI (105 mg, 0.55 mmol), Et_3N (155 µL, 1.1 mmol) and **Intermediate12** (144 mg, 0.5 mmol) were successively added. The mixture was stirred at rt for 24 hours and was diluted with EtAOc and washed with a sat. $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The product was then purified by flash chromatography on silica gel (CH_2CL_2/AcOEt = 95/5) to afford the title compound as 140 mg of a pale oil.

Yield: 57%

^1H NMR ($CDCl_3$) : δ 7.30 (d, 2H) ; 7.23 (d, 2H) ; 7.01-7.13 (m, 3H) ; 6.84 (s, 1H) ; 6.61 (d, 1H) ; 4.51 (d, 2H) ; 4.23 (q, 2H) ; 3.85 (s, 3H) ; 2.52 (d, 2H) ; 2.21 (s, 3H) ; 1.90 (hept, 1H) ; 1.57 (s, 6H) ; 1.25 (t, 3H) ; 0.93 (d, 6H).



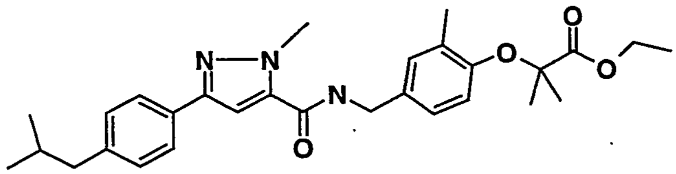
Example 7

2-methyl-2-[(2-methyl-4-{[({1-methyl-5-[4-(2-methylpropyl) phenyl]-1*H*-pyrazol-3-yl} carbonyl) amino] methyl} phenyl) oxy]propanoic acid.

Intermediate 38 (130 mg, 0.26 mmol) was dissolved in 2 mL of THF and 5 mL of ethanol and 2.6 mL of 1N NaOH (2.6 mmol) were added. The solution was heated to 80°C for 24 hours and concentrated under vacuum. The residue was acidified with 1N HCl and the white solid was filtered off and dried under reduced pressure at 50°C to provide the title carboxylic acid as 116 mg of a white powder.

Yield : 96%

^1H NMR ($CDCl_3$) : δ 7.30 (d, 2H) ; 7.22 (d, 2H) ; 7.17 (s, 1H) ; 7.06 (dd, 1H) ; 6.85 (s, 1H) ; 6.78 (d, 1H) ; 4.52 (d, 2H) ; 3.85 (s, 3H) ; 2.51 (d, 2H) ; 2.23 (s, 3H) ; 1.90 (hept, 1H) ; 1.60 (s, 6H) ; 1.25 (t, 3H) ; 0.93 (d, 6H).



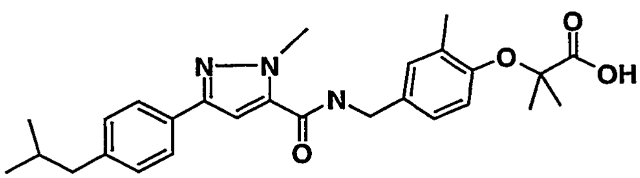
Intermediate 39

Ethyl 2-methyl-2-[(2-methyl-4-{[({1-methyl-3-[4-(2-methylpropyl) phenyl]-1*H*-pyrazol-5-yl} carbonyl) amino]methyl} phenyl) oxy] propanoate.

Intermediate 37 (142 mg, 0.55 mmol) was dissolved in 3 mL of DMF, HOBT (75 mg, 0.55 mmol), EDCI (105 mg, 0.55 mmol), Et_3N (155 µL, 1.1 mmol) and **intermediate 12** (144 mg, 0.5 mmol) were successively added. The mixture was stirred at rt for 24 hours and was diluted with EtAOc and washed with a sat. $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The product was then purified by flash chromatography on silica gel (CH_2CL_2/AcOEt = 95/5) to afford the title compound as 205 mg of a pale oil.

Yield: 83%

^{1}H NMR ($CDCl_3$) : δ 7.63 (d, 2H) ; 7.14 (d, 2H) ; 7.11 (m, 1H) ; 7.01 (dd, 1H) ; 6.72 (s, 1H) ; 6.62 (d, 1H) ; 6.31 (t, 1H) ; 4.47 (d, 2H) ; 4.23 (q, 2H) ; 4.21 (s, 3H) ; 2.47 (d, 2H) ; 2.22 (s, 3H) ; 1.86 (hept, 1H) ; 1.58 (s, 6H) ; 1.25 (t, 3H) ; 0.89 (d, 6H).

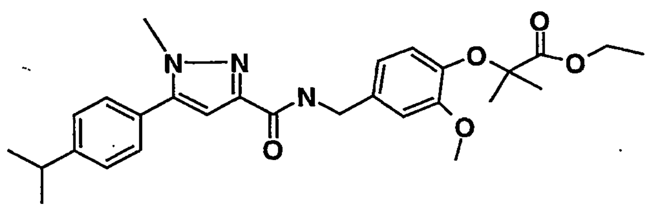


Example 8

2-methyl-2-[(2-methyl-4-{[({1-methyl-3-[4-(2-methylpropyl) phenyl]-1*H*-pyrazol-5-yl} carbonyl) amino] methyl} phenyl) oxy]propanoic acid.

Intermediate 39 (202 mg, 0.41 mmol) was dissolved in 2 mL of THF and 15 mL of ethanol and 4.1 mL of 1N NaOH (4.1 mmol) were added. The solution was heated to 80°C for 2.5 hours and concentrated under vacuum. The residue was diluted in 10 mL of water and acidified with 1N HCl and the white solid was filtered off and

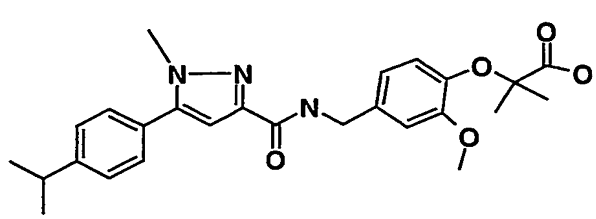
dried under reduced pressure at 50°C to provide the title carboxylic acid as 185 mg of a white powder.
Yield : 97%
[1]H NMR ($CDCl_3$) : δ 7.63 (d, 2H) ; 7.15 (m, 3H) ; 7.05 (m, 1H) ; 6.78 (m, 1H) ; 6.72 (s, 1H) ; 6.30 (t, 1H) ; 4.49 (d, 2H) ; 4.21 (s, 3H) ; 2.47 (d, 2H) ; 2.24 (s, 3H) ; 1.86 (hept, 1H) ; 1.62 (s, 6H) ; 0.89 (d, 6H).



Intermediate 40

Ethyl 2-methyl-2-{[4-{[({1-methyl-5-[4-(1-methylethyl)phenyl]-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}propanoate.

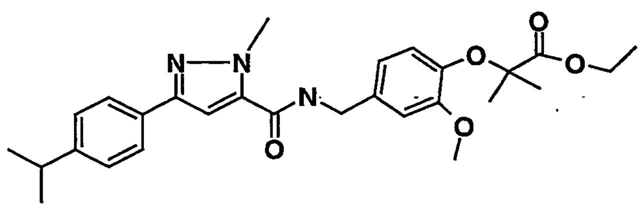
Intermediate 20 (105 mg, 0.43 mmol) was dissolved in 3 mL of DMF, HOBT (58 mg, 0.43 mmol), EDCI (82 mg, 0.43 mmol), Et_3N (120 μL, 0.86 mmol) and **Intermediate 15** (144 mg, 0.5 mmol) were successively added. The mixture was stirred at rt for 24 hours and was diluted with EtAOc and washed with a sat. $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The product was then purified by flash chromatography on silica gel (CH_2CL_2/AcOEt = 95/5) to afford the title compound as 205 mg of a pale oil.
Yield: 83%
[1]H NMR ($CDCl_3$) : δ 7.63 (d, 2H) ; 7.14 (d, 2H) ; 7.11 (m, 1H) ; 7.01 (dd, 1H) ; 6.72 (s, 1H) ; 6.62 (d, 1H) ; 6.31 (t, 1H) ; 4.47 (d, 2H) ; 4.23 (q, 2H) ; 4.21 (s, 3H) ; 2.47 (d, 2H) ; 2.22 (s, 3H) ; 1.86 (hept, 1H) ; 1.58 (s, 6H) ; 1.25 (t, 3H) ; 0.89 (d, 6H).



Example 9

2-methyl-2-{[4-{[({1-methyl-5-[4-(1-methylethyl)phenyl]-1*H*-pyrazol-3-yl} carbonyl)amino]methyl}-2-(methyloxy) phenyl]oxy} propanoic acid.

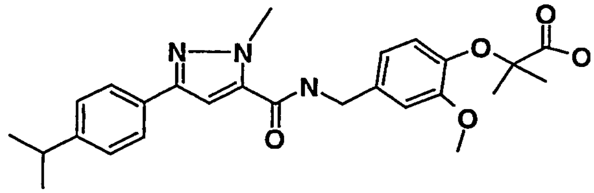
2.9 mL of NaOH (1N) was added to a solution of 145 mg of **Intermediate 40** in 1mL of THF and 5 mL of EtOH and heated at 80°C for 2h.
After evaporation of the solvent, the residue was dissolved in water and the solution acidified with HCl (1N). The solid formed was collected by filtration.
Yield= 70%
^{1}H NMR ($CDCl_3$) : δ 7.25 (s, 2H); 4.18 (s, 2H); 6.88 (m; 3H); 6.78 (s, 1H); 4.53 (d; 2H); 3.80 (d, 6H); 2.89 (spt, 1H); 1.43 (s, 6H); 1.22 (s, 3H); 1.20 (s, 3H); 1.18



Intermediate 41
Ethyl 2-methyl-2-{[4-{[({1-methyl-3-[4-(1-methylethyl)phenyl]-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-(methyloxy) phenyl]oxy} propanoate.

74 mg of HOBT, 105 mg of EDCI, 155μL of Et_3N and then 152 mg of **Intermediate 15** was added to a solution of 134 mg of **Intermediate 18** in 5 mL of DMF.
After 70h, the solvent was evaporated and the residue dissolved in ethylacetate.
The organic layer was washed successively by K_2CO_3, HCl (1N) and brine.

The solid obtained was purified by chromatography (Dichloromethane/ Ethylacetate 90/10).
Yield= 62%
^{1}H NMR ($CDCl_3$) : δ 7.55 (d, 2H) ; 7.12 (d, 2H) ; 6.91 (t, 1H) ; 6.80 (s, 1H) ; 6.67 (m, 3H) ; 4.40 (d, 2H) ; 4.13(q, 2H) ; 4.11 (s, 3H) ; 3.62 (s, 3H) ; 2.80 (sept, 1) ; 1.45(s, 6H) ; 1.17 (t, 3H) ; 1.15 (d, 6H)

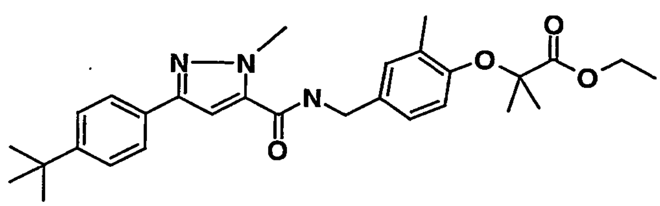


Example 10

2-methyl-2-{[4-{[({1-methyl-3-[4-(1-methylethyl)phenyl]-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-(methyloxy) phenyl]oxy} propanoic acid.

2 mL of EtOH and 1.3 mL of NaOH (1N) was added to a solution of 64 mg of **Intermediate 41** in THF.

After 50 min at 80°C, the solvents were evaporated. The yellow solid obtained was dissolved in water, acidified with HCl (1N) until formation of a white solid. The solid was filtered and purified by chromatography (Dichloromethane/ Methanol; from 95/5 to 80/20).
The residue was then, dissolved in ethylacetate, washed with HCl (1N) and brine; dried on Na_2SO_4.
Yield: 53%
^1H NMR ($CDCl_3$): δ 7.60 (d, 2H) ; 7.18 (d, 2H) ; 6.90 (m, 3H) ; 6.69 (s, 1H) ; 6.31 (m, 1H) ; 4.52 (2H) ; 4.17 (s, 3H) ; 3.84 (s, 3H) ; 2.85 (spt, 1H) ; 1.45 (s, 6H) ; 1.18 (s, 6H)

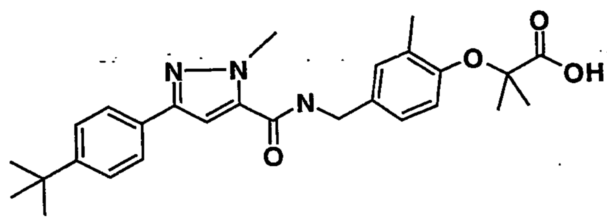


Intermediate 42

Ethyl 2-[(4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-methylphenyl)oxy]-2-methylpropanoate.

To a solution of 3g **Intermediate 5** in 5mL of DMF, was added successively, 1.57g of HOBT, 2.22g of EDCI, 3.25 mL of Et_3N and then 3.12g of **Intermediate 12**. After

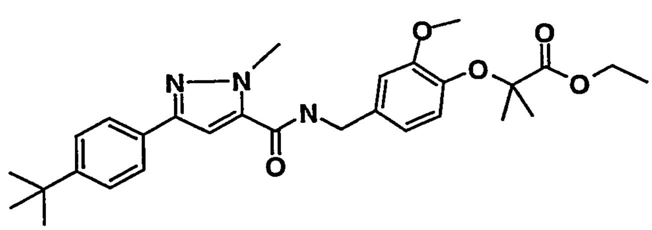
stirring the solution for 24h, the organic layer was extracted with ethylacetate, washed with brine, NaOH (0.5 N) and brine.
The solid obtained was purified by chromatography (Dichloromethane/Ethylacetate 95/5) to give a white solid.
Yield= 73%
^1H NMR ($CDCl_3$) : δ 7.81 (d, 2H) ; 7.55 (d,2H) ; 7.27 (s,1H) ; 7.16 (d, 1H) ; 6.87 (s, 1H) ; 6.78 (d, 1H) ; 6.41 (m, 1H) ; 4.64 (d, 2H) ; 4.40 (t, 2H) ; 4.37 (s, 3H) ; 2.38 (s, 3H) ; 1.74 (s, 6H) ; 1.47 (s,9H) ; 1.41 (t, 3H)



Example 11

2-[(4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-methylphenyl)oxy]-2-methylpropanoic acid.

73 mL of NaOH (1N) was added to a solution of 3.69g of **Intermediate 42** in 50mL of THF and 5mL of EtOH.
The reaction mixture was heated at 80°C for 1h30 and concentrated under vacuum.
30mL of water was added and the solution acidified by a dropwise addition of HCl (1N).
The white solid was collected by filtration and dried at 50°C under vacuum.
Yield= quantitative
^1H NMR ($CDCl_3$): δ 7.58 (d, 2H); 7.31 (d, 2H); 7.08 (s,1H); 6.98 (d, 1H); 6.71 (d, 1H); 6.94 (s, 1H); 6.25 (m, 1H); 4.42 (d, 2H); 4.14 (s, 3H); 2.17 (s, 3H); 1.55 (s, 6H); 1.25 (s, 9H)



Intermediate 43

Ethyl 2-{[4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}-2-methylpropanoate .

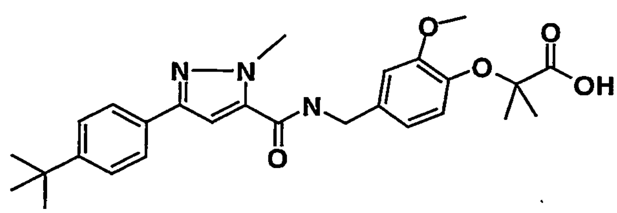
310 µL of $SOCl_2$ was added to a solution of 220 mg **Intermediate 5** in toluene is added.

The reaction mixture was heated at 100°C for 3h, evaporated to dryness. The residue was diluted in toluene and evaporated again.

The yellow oil obtained was diluted in CH_2Cl_2 anhydrous then added to a stirred solution of 284 mg of **Intermediate 15** in CH_2Cl_2 with 370µL of Et_3N under nitrogen. The reaction mixture was stirred at room temperature overnight, then washed twice with HCl (1N) and once with $NaHCO_3$. The organic layer was dried on Na_2SO_4 and filtered to give after evaporation to dryness the title compound as a pale oil.

Yield= quantitative

^{1}H NMR ($CDCl_3$) : δ 7.60 (d, 2H) ; 7.33 (d, 2H) ; 6.73 (m, 4H) ; 6.48 (m, 1H) ; 4.44 (d, 2H) ; 4.16 (q, 2H) ; 4.15(s, 3H) ; 3.70 (s, 3H) ; 1.48 (s, 6H) ; 1.25 (s, 9H) ; 1.20 (t, 3H)



Example 12

2-{[4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}-2-methyl propanoic acid.

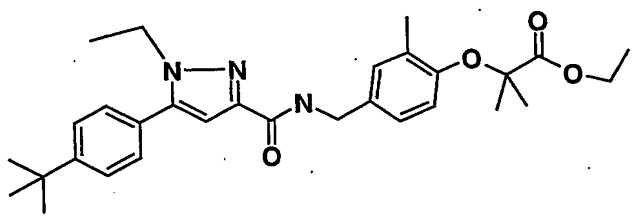
1.3 mL of NaOH (1N) was added to a solution of 435 mg of **Intermediate 43** in EtOH.

After 3h at 80°C, the reaction was not complete; so 1.3 mL of NaOH (1N) was added and the solution heated for 1h at 85°C; the reaction was still not complete so 1.3 mL of NaOH (1N) was added and the reaction heated at the same temperature for 1h. The reaction mixture was evaporated, and HCl (1N) added. The white off precipitate was triturated and filtered.

Yield= quantitative

Mp=102-105°C; gummy

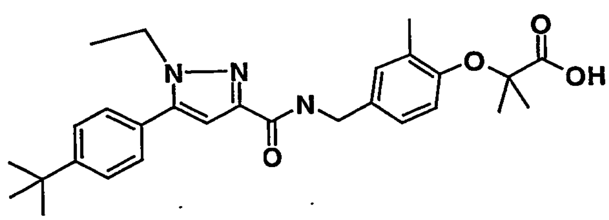
^1H NMR (DMSO): δ 9.02 (m, 1H); 7.67 (d, 2H); 7.45 (d, 2H); 7.29 (s, 1H), 6.99 (s, 1H); 6.80 (s, 2H); 4.40 (d, 2H), 4.11 (s, 3H); 3.74 (s, 3H); 1.44 (s, 6H); 1.30 (s, 9H)



Intermediate 44

Ethyl 2-[(4-{[({5-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-methylphenyl)oxy]-2-methylpropanoate

To a solution of 208 mg (0.765 mmol) of **Intermediate 30** in DMF was added successively 103 mg of HOBT, 146 mg of EDCI, 214 μL of Et_3N and 200 mg of **Intermediate 12.** After stirring for 5h, the mixture was concentrated, diluted in ethylacetate and washed twice with $NaHCO_3$, once with HCl (1N) and brine. The organic layer was dried on Na_2SO_4, filtered and evaporated to dryness.
The residue was purified by chromatography (Dichloromethane/Ethylacetate 99/1) to give the title compound as a slightly white oil.
Yield=74%
^1H NMR ($CDCl_3$) : δ 7.40 (d, 2H) ; 7.24 (d, 2H) ; 7.09 (s, 2H) ; 6.97 (d, 1H) ; 6.74 (s, 1H) ; 6.56 (d , 1H) ; 4.46 (d, 2H) ; 4.17 (q, 2H) ; 4.07 (q, 2H) ; 2.15 (s, 3H) ; 1.51 (s, 6H) ; 1.34 (t, 3H) ; 1.29 (s, 9H) ; 1.19 (t, 3H)



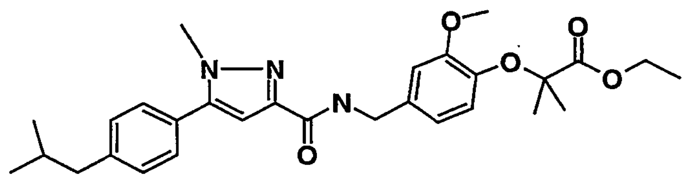
Example 13

2-[(4-{[({5-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-methylphenyl)oxy]-2-methylpropanoic acid.

EtOH then 4.9 mL of NaOH (1N) was added to a solution of 250 mg (0.49 mmol) of **Intermediate 44** in THF. After stirring the mixture at 80°C during 1h30, solvent was removed by vacuum to obtain a yellow solid which was put in water and acidified with HCl (1N) to give a white solid which was filtered and dried.

Yield= 51%

1H NMR ($CDCl_3$): δ 7.26 (d, 2H); 7.95 (d, 2H); 6.97 (s, 1H); 6.82 (d, 1H); 6.60 (d, 1H); 6.56 (d, 1H); 4.31 (d, 2H), 4.93 (q, 2H); 2.02 (s, 3H); 1.40 (s, 6H); 1.19 (t, 3H), 1.15 (s, 9H)



Intermediate 45

Ethyl 2-methyl-2-{[4-{[({1-methyl-5-[4-(2-methylpropyl)phenyl]-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-(methyloxy) phenyl] oxy}propanoate.

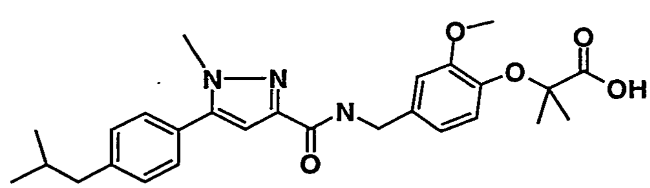
To a solution of 142 mg **Intermediate 36** in 1mL of DMF was added successively 75 mg of HOBT, 105 mg of EDCI, 155μL of Et_3N and 142 mg of 152 mg (0.5mmol) of **Intermediate 15.**

After stirring for 24h, the organic layer was extracted with ethylacetate, washed with brine, dried on Na_2SO_4, filtered and evaporated to dryness.

The residue was purified by chromatography (Dichloromethane/Ethylacetate 90/10) to give the title compound as a thick oil.

Yield=53%

^{1}H NMR ($CDCl_3$) : δ 7.25 (d, 2H) ; 7.15 (d, 2H) ; 7.1 (m, 1H) ; 6.8 (s, 1H) ; 6.75 (m, 3H) ; 4.45 (d, 2H) ; 4.15 (q, 2H) ; 3.8 (s, 3H) ; 3.7 (s, 3H) ; 2.55 (d, 2H) ; 1.8 (m, 1H) ; 1.5, (s, 6H) ; 1.2 (t, 3H) ; 0.9 (d, 6H)



Example 14

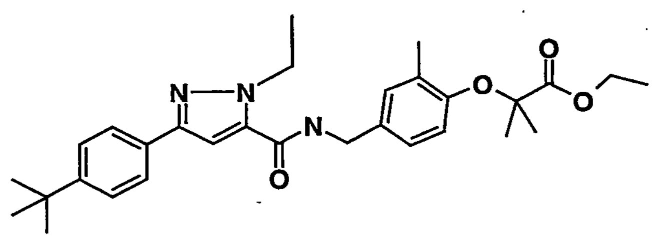
2-methyl-2-{[4-{[({1-methyl-5-[4-(2-methylpropyl)phenyl]-1*H*-pyrazol-3-yl} carbonyl)amino]methyl}-2-(methyloxy) phenyl] oxy}propanoic acid.

5 mL of EtOH and 2.6 mL of NaOH (1N) was added to a solution of 135 mg (0.266 mmol) of **Intermediate 45** in 2 mL of THF.

After stirring at 80°C for 24h the mixture was concentrated, acidified with HCl (1N) to give after filtration a white solid which was washed with water and dried under vacuum.

Yield=93%

^{1}H NMR ($CDCl_3$): δ 7.23 (d, 2H); 7.15 (d, 2H); 6.85 (m, 3H); 6.78 (s, 1H); 4.52 (d, 2H); 3.81 (s, 3H); 3.80 (s, 3H); 2.45 (d, 2H); 1.83 (hept, 1H); 1.43 (s, 6H); 0.86 (d, 6H)



Intermediate 46

Ethyl 2-[(4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-methylphenyl)oxy]-2-methyl propanoate.

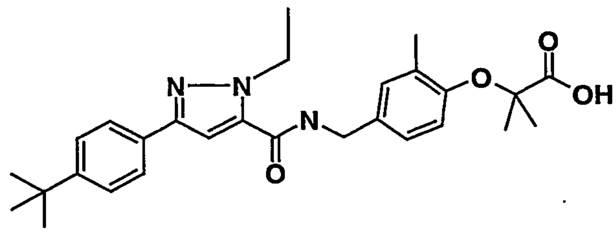
To a solution of 208 mg (0.765 mg) of **Intermediate 29** in DMF was added successively 103 mg of HOBT, 146 mg of EDCI, 214μL of Et_3N and 200mg of **Intermediate 12.**

After stirring 5h, the mixture was concentrated, dissolved in ethylacetate, washed twice with $NaHCO_3$, once with HCl (1N) and brine, dried on Na_2SO_4, filtered and concentrated to dryness.

The residue was purified by chromatography (Dichloromethane/Ethylacetate 99/1) to give the title compound as white crystal.

Yield= 82%

^{1}H NMR ($CDCl_3$) : δ 7.6 (d, 2H) ; 7.35 (d, 2H) ; 7.08 (s, 1H) ; 6.98 (d, 1H) ; 6.62 (s, 1H) ; 6.56 (d, 1H) ; 6.2 (m, 1H) ; 4.6 (q, 2H) ; 6.43 (d, 2H) ; 4.2 (q, 2H) ; 2.19 (s, 3H) ; 1.5 (s, 6H) ; 1.41 (t, 3H) ; 1.26 (s, 9H) ; 1.2 (t, 3H)



Example 15

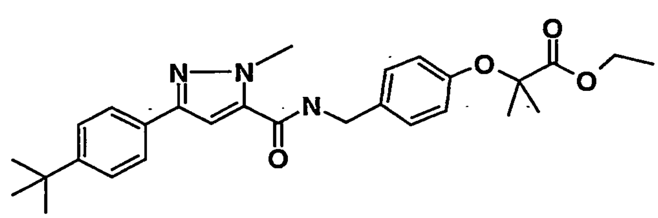
2-[(4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-methylphenyl)oxy]-2-methyl propanoic acid.

5 mL of absolute ethanol and 5.5 mL of NaOH (1N) was added to a solution of 279 mg (0.55 mmol) of **Intermediate 46** in THF.

After stirring at 80°C for 1h20, the mixture was concentrated to give a yellow solid which was dissolved in water and acidified with HCl (1N) to give a pale yellow solid after filtration.

Yield=80%

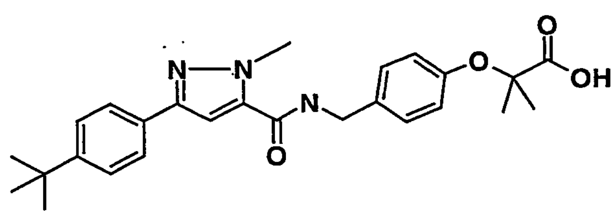
^{1}H NMR ($CDCl_3$): δ 7.47 (d, 2H); 7.20 (d, 2H); 6.96 (s, 1H); 6.87 (d, 1H); 6.61 (d, 1H); 6.50 (s, 1H); 6.11 (m, 1H); 4.44 (q, 2H); 4.30 (d, 2H); 2.05 (s, 3H); 1.42 (s, 6H); 1.29 (t, 3H); 1.12 (s,9H)



Intermediate 47

Ethyl 2-[(4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}phenyl)oxy]-2-methyl propanoate.

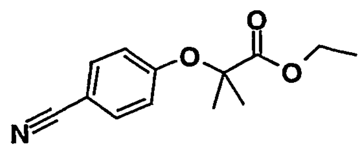
To a solution of 6.52g (0.025 mol) of **Intermediate 5** in 165 mL of CH_2Cl_2 and 165 mL of DMF was added 3.41 g of HOBT, 4.84 g of EDCI, 3.6 mL of Et_3N and is stirred for 15 minutes. A solution of 5 g of **Intermediate 49** dissolved in 10 mL of CH_2Cl_2 was added dropwise to the mixture and stirred at room temperature for 3 days. Then water was added ; the organic layer extracted twice with CH_2Cl_2, and washed with Na_2CO_3, water, HCl (1N), water and brine. After evaporation to dryness, the residue was purified by chromatography (CH_2Cl_2/MeOH 98/2) to give the title compound as a yellow oil.
Yield=52%
^{1}H NMR ($CDCl_3$) : δ 7.61 (d, 2H) ; 7.34 (d, 2H) ; 7.16 (d, 2H) ; 6.77 (d, 2H) ; 6.66 (s, 1H) ; 6.18 (m, 1H) ; 4.47 (d, 2H) ; 4.16 [(s, 3H) + (q, 2H)] ; 1.53 (s, 6H) ; 1.26 (s, 9H) ; 1.19 (t, 3H)



Example 16

2-[(4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}phenyl)oxy]-2-methylpropanoic acid

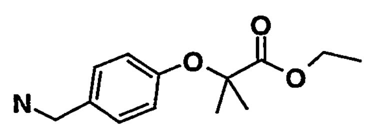
21.8 mL of NaOH (1N) was added to a solution of 5.2 g (11 mmol) of **Intermediate 47** in 100mL of EtOH.
After stirring at 70°C for 3h, the mixture was concentrated, dissolved in water and washed with ethylacetate. The aqueous layer was acidified with a 1N HCl solution until pH=5, extracted with 150 mL of CH_2Cl_2. The white precipitate formed in the organic layer was filtered and washed with water and pentane.
The organic layer was concentrated to dryness, triturated in water with a little of Et_2O, filtered, and washed with water and pentane to give a white solid.
Both white solids were combined to give a single batch of the title compound.
Yield=85%
Mp=154.6°C
^{1}H NMR (DMSO): δ 9.02 (s, 1H); 7.68 (d, 2H); 7.45 (d,2H); 7.28 (s,1H); 7.24 (d, 2H); 6.81 (d, 2H); 4.39 (d, 2H); 4.11 (s, 3H); 1.50 (s, 6H); 1.30 (s, 9H)



Intermediate 48

Ethyl 2-[(4-cyanophenyl)oxy]-2-methylpropanoate.

To a solution of 25.05g (0.210 mol) of **4-cyanophenol** in 250 mL of acetonitrile was added 56.66g of K_2CO_3, then refluxed for 1h.
At this temperature 61.74 mL of **ethyl-2-bromo-isobutyrate** was added dropwise.
After two days at reflux, 0.5eq of **ethyl-2-bromo-isobutyrate** was added dropwise, followed by 0.5 eq of K_2CO_3.
After 24h at reflux, the mixture was filtered, then evaporated to dryness. 100 mL of NaOH (1N) was added to the residue, and the organic layer extracted with 150 mL of Et_2O, twice with 75 mL of Et_2O, then washed with 100 mL and 50 mL of NaOH (1N) and 100 mL of brine.
The organic layer was then dried on $MgSO_4$, filtered and evaporated to dryness.
The oil obtained was diluted in 200 mL of $^iPr_2O$ and filtered to give the title compound as a yellow oil.
Yield= quantitative.
^1H NMR ($CDCl_3$): δ 7.47 (d, 2H); 6.78 (d, 2H); 4.15 (q, 2H); 1.58 (s, 6H); 1.14 (t, 3H)



Intermediate 49

Ethyl 2-{[4-(aminomethyl)phenyl]oxy}-2-methylpropanoate.

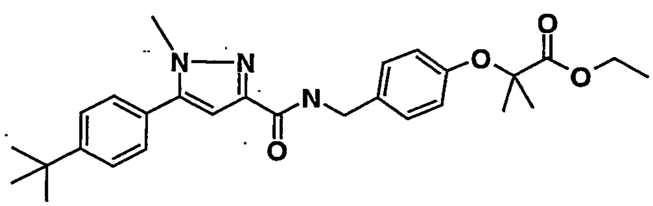
4.73 g (7.5% w/w) Pd/c 10% under 3 Bars was added to a solution of 63.1g (0.27 mol) of **Intermediate 48** in 80 mL of AcOH and 160 mL of EtOH under nitrogen.
After 6h under hydrogene, the reaction was not complete; the mixture was filtered through a Whatmann filter, evaporated to dryness and dissolved in the same

volumes of solvent and same quantity of Pd/c but under 3 Bars at 50°C. After 6h under hydrogene, the reaction was complete.

The mixture was filtered through a Whatmann filter and evaporated to dryness, diluted in 400 mL H_2O and 400 mL AcOEt, stirred for 5 minutes, extracted with 260 mL H_2O, acidified with a concentrated HCl solution, washed with 260 mL of EtOAc. At 10°C, the aqueous solution was reduced to pH8 with NaOH (37%). 400mL of CH_2Cl_2 were added to the solution which was stirred for 5 minutes, then extracted twice with 200mL of CH_2Cl_2, dried on $MgSO_4$, filtered and evaporated to dryness to give the title compound as a yellow oil.

Yield= 15%

^{1}H NMR ($CDCl_3$): δ 7.18 (d, 2H); 6.82 (d, 2H); 4.24 (q, 2H); 2.08 (s, 1H); 1.93 (s, 1H); 1.59(s, 6H); 1.26 (s, 3H)



Intermediate 50

Ethyl 2-[(4-{[({5-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}phenyl)oxy]-2-methyl propanoate.

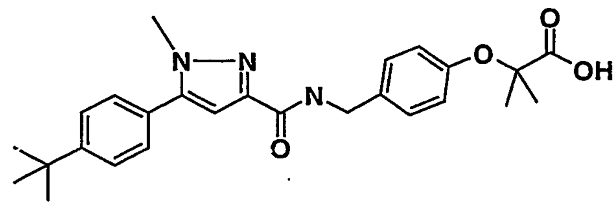
To a solution of 5.11 g **Intermediate 3** in 165 mL of CH_2Cl_2 and 165 mL of DMF was added 2.676 g of HOBT, 3.79 g of EDCI and 2.8 mL of Et_3N. The mixture was stirred at room temperature for 15 minutes, then 3.92 g of **Intermediate 49** diluted in 8 mL of CH_2Cl_2 were added dropwise.

After 3 days at 22°C, 170 mL of water were added to the reaction mixture. The organic layer was extracted twice with 90 mL of CH_2Cl_2, then washed successively with 170 mL of Na_2CO_3, 170 mL of water, 170 mL of HCl (1N), 170 mL of water, 170 mL of brine, then dried on $MgSO_4$, filtered and evaporated to dryness.

The mixture was purified by chromatography (CH_2Cl_2/MeOH 99/1 to 98/2), to give the title compound.

Yield=18%

^{1}H NMR ($CDCl_3$): δ 7.51 (d, 2H); 7.37 (d, 2H); 7.29 (d, 2H); 6.84 (d, 2H); 4.59 (d, 2H); 4.25 (t, 2H); 3.89 (s, 3H); 1.61 (s, 6H); 1.38 (s, 9H); 1.28 (q, 3H)



Example 17

2-[(4-{[({5-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}phenyl)oxy]-2-methylpropanoic acid.

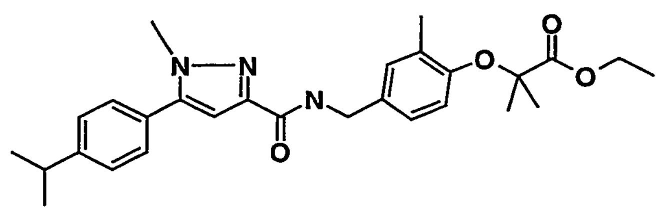
13.4 mL of NaOH (1N) was added to a solution of 3.2 g (6.7 mmol) of **Intermediate 50** in 64 mL of EtOH.

After 1h10 at 70°C, the mixture was allowed to go to room temperature, then 50 mL of water was added and the organic layer extracted twice with 25 mL of AcOEt. The aqueous layer was acidified with HCl (1N) and the organic layer extracted with 30 mL of CH_2Cl_2, dried on $MgSO_4$, filtered and evaporated to dryness to give the title compound as a white solid.

Yield=88%

Mp= 70°C (gummy)

^{1}H NMR ($CDCl_3$): δ 7.41 (d, 2H); 7.27 (m,, 3H); 7.19 (s, 1H); 6.82 (m, 3H); 4.50 (s , 2H); 3.80 (s, 3H); 1.52 (s, 6H); 1.29 (s, 9H)



Intermediate 51

Ethyl-2-methyl-2-[(2-methyl-4-{[({1-methyl-5-[4-(1-methylethyl)phenyl]-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}phenyl)oxy] propanoate.

To a solution of 105 mg (0.43 mmol) of **Intermediate 20** in 3 mL of DMF was added successively 58 mg of HOBT, 82 mg of EDCl, 120 μL of Et_3N and 113 mg of **Intermediate 12.**

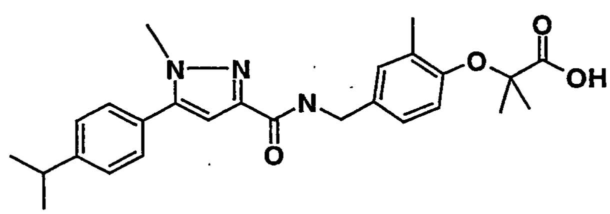
The reaction mixture was stirred for 24h at room temperature, extracted with ethylacetate, washed with brine, dried on Na_2SO_4 and evaporated to dryness.

The residue was purified by chromatography (Dichloromethane/ethyl- acetate 95/5).

Yield=78%

Mass AP^+=478.27

^{1}H NMR ($CDCl_3$) : δ 7.25 (s, 4H) ; 7.07 (d, 1H) ; 6.96 (d, 1H) ; 6.77 (s, 1H) ; 6.55 (d, 1H) ; 4.45 (d, 2H) ; 4.17 (quad, 2H), 3.78 (s, 3H) ; 2.89 (sept, 1H) ; 2.14 (s, 3H) ; 1.51 (s, 6H) ; 1.21 (d, 6H) ; 1.19 (t, 3H)



Example 18

2-methyl-2-[(2-methyl-4-{[({1-methyl-5-[4-(1-methylethyl)phenyl]-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}phenyl)oxy]propanoic acid.

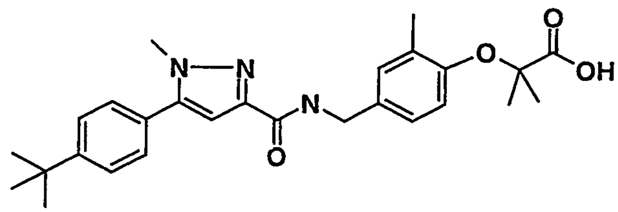
2.9 mL of NaOH (1N) was added to a solution of 140 mg (0.29 mmol) of **Intermediate 51** (ethyl-2-methyl-2-[(2-methyl-4-{[({1-methyl-5-[4-(1-methylethyl)phenyl]-1*H*-pyrazol-3-yl}carbonyl) amino]methyl}phenyl)oxy](in 1mL of DMF and 5 mL of EtOH.

The reaction mixture was heated at 80°C for 2h ; then evaporated to dryness, dissolved in water, acidified with HCl (1N) ; a white precipitate appeared which was filtered.

Yield= 88%

^{1}H NMR ($CDCl_3$) : δ 7.12 (s, 4H) ; 7.06 (s, 1H) ; 6.96 (s, 1H) ; 6.82 (d, 1H) ; 6.65 (s, 1H) ; 6.57 (d, 1H) ; 4.31 (d, 2H) ; 3.65 (s, 3H) ; 2.76 (sept, 1H) ; 2.02 (s, 3H) ; 1.41 (s, 6H) ; 1.08 (d, 6H).

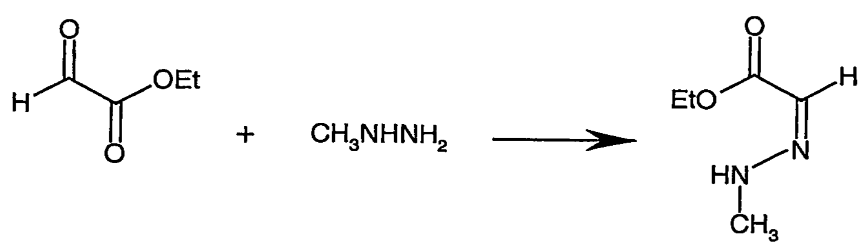
Example 1



2-[(4-{[({5-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-methylphenyl)oxy]-2-methylpropanoic acid

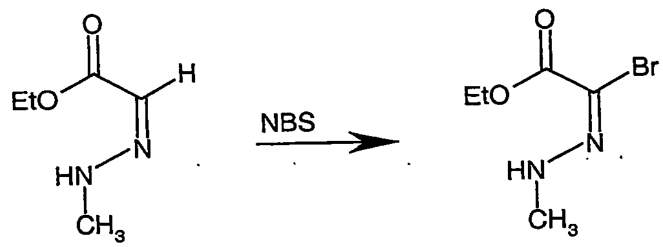
This compound was also prepared by the method disclosed in Scheme 3 as follows.

Preparation of the Intermediate of formula III



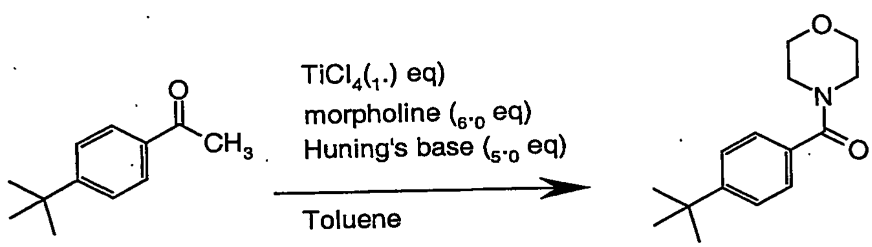
Intermediate a

[Methylhydrazono] acetic acid ethyl ester. Methyl hydrazine (50 mL, 0.94 mol, 1.0 eq) was dissolved in toluene and cooled to 10°C. Ethyl glyoxylate (50% solution in toluene, 200.5 g of the solution, 1.03 mol, 1.1 eq) was added dropwise maintaining the temperature below 25°C. THF (50 mL) was used to rinse the addition funnel and was added to the reaction mixture. The reaction was heated to 50°C for 5 h. At temperature, THF and any volatiles (i.e. methyl hydrazine or toluene) was distilled off and heptanes was added to the reaction mixture. The reaction was cooled to 5-10°C during which time, solids began to precipitate out. After 1 h held at 0°C, the reaction was filtered and the cake washed with tbme/heptanes. Product is a pink to purple solid (isolated 93 g, 77% yield, 96% HPLC purity).



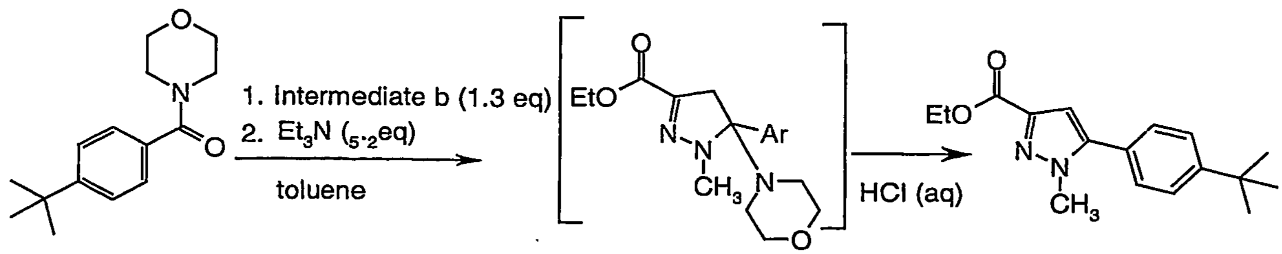
Intermediate b

Bromo[methylhydrazono] acetic acid ethyl ester. N-Bromosuccinimide (34.2 g, 0.19 mol, 1.0 eq.) was added as a solid in portions to a slurry of Intermediate a (25g, 0.19 mol, 1.0 eq.)in ethyl acetate (125 mL) so as to maintain the temperature at less than 25°C. The reaction was stirred at 5-10°C for 1 h. Once the reaction was deemed complete, it is filtered and the cake was washed with ethyl acetate (75 mL) which was added to the filtrate. The combined filtrate and wash were bottled and stored at 5-10°C for use in the next step. Yield was > 95% solution yield via HPLC.



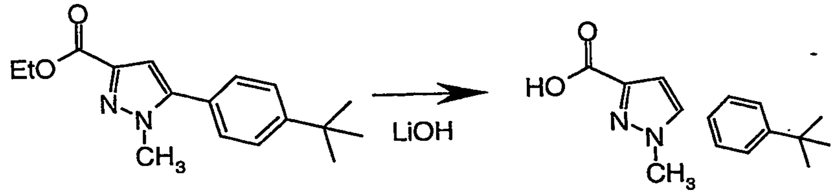
Intermediate c

4-[1-(4- tert-butyl-phenyl)-vinyl]-morpholine. Morpholine was added to slurry of toluene (60 mL) and sodium sulfate (50 g, which served as a mechanical abrasive and flocculent) at 5°C. Titanium tetrachloride (30 mL, 0.34 mol, 6.0 eq was added dropwise to form a light green slurry (titanium tetrachloride – morpholine complex). Hunig's base (48 mL, 0.28 mol, 5.0 eq) was added followed by t-butyl acetophenone (10.0 g, 0.056 mol, 1.0 eq). The ice bath was removed and the reaction was heated to 70°C for 3 h. Once the reaction was deemed complete, it was cooled to 20°C and filtered. The cake was washed with toluene which was added to the filtrate. The filtrate (containing Intermediate c) was drummed out for use in the next step. The cake was quenched with water and discarded. The aqueous filtrate was also discarded. Solution yield was > 95% via GC.



Intermediate d

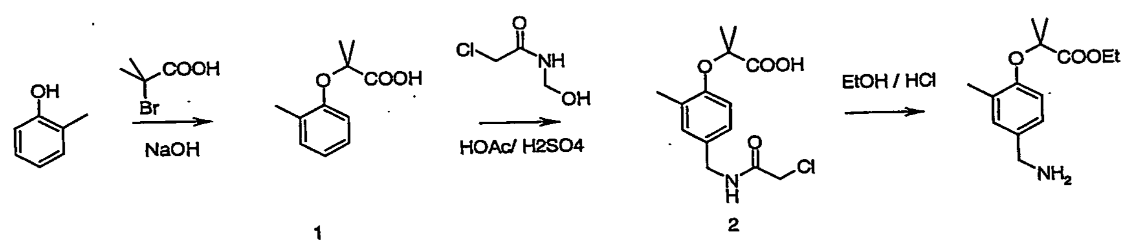
1-Methyl-5-(4-tert-butylphenyl)-2*H*-pyrazole-3-(carboxylic acid ethyl ester). The toluene solution of t-butyl acetophenone enamine Intermediate c (0.14 mol, 34.8 g, 1.0 eq) from the previous step was distilled under reduced pressure until the morpholine and Hunig's base content was less than *< 10 mol% each with respect to* Intermediate c. To the resulting concentrated solution of Intermediate c was added ethyl acetate (210 mL) and triethylamine (115 mL, 0.82 mol, 5.8 eq) at ambient temperature. The mixture was heated to 40°C at which time an ethyl acetate (210 mL) solution of Intermediate b (43.0 g, 0.21 mmol, 1.45 eq) was added dropwise over half an hour. The reaction was held at 40 °C for an additional 3.5 h. After the reaction was deemed complete, the reaction was cooled to 0-5°C and 4N HCl (284 mL, 1.1 mol, 8.0 eq) was added dropwise so as to maintain the temperature below 30°C. After acidification was complete, the mixture stirred for an additional hour at 20°C. The phases were allowed to separate and aqueous layer discarded. The organic layer was washed with fresh water (150 mL) and then separated via phase cut. The organic layer was distilled under reduced pressure to remove ethyl acetate in preparation for the hydrolysis step. Solution yield is approximately 80-85%. Alternatively, Intermediate d maybe isolated from the organic phase by precipitation from toluene/ethyl acetate/heptanes.



<u>**Intermediate e**</u>

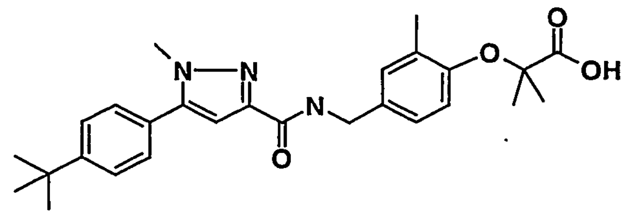
1-Methyl-5-(4-tert-butylphenyl)-2*H*-pyrazole-3-(carboxylic acid). To a solution of pyrazole ester Intermediate d in toluene was added THF (150 mL). LiOH (17.9 g, 0.43 mol, 4 eq.) in 180 mL water was added and the reaction was heated to 60°C for 4-6 h. After the reaction was deemed complete, the THF (150-200 mL) was distilled off. TbMe (150mL) was added and water (100 mL) was added and stirred and the phases cut. The aqueous layer (containing the lithium salt of Intermediate e) was washed with fresh tbMe (120 mL, to remove any remaining organic impurities) and then phase cut. Isopropanol (30 mL) was added to the aqueous layer which was acidified to pH = 1 with 6N HCl (85 mL). During the acidification, white/yellow solids precipitate out. After filtration, the cake was washed with water (100 mL) followed by a wash with tBME/heptanes (10:90). Isolated yield was 21.0 g, ~81% from Intermediate d.

<u>**Intermediate f**</u>



Cresol was reacted with α-bromoisobutyric acid in the presence of NaOH to give acid 1, which was then amidomethylated using N-hydroxymethyl chloroacetamide in HOAc/H_2SO_4 to afford acid-amide 2. The amide was alcoholyzed in ethanol using HCl gas with concomitant ester formation to give the desired product Intermediate f.

Intermediate f and Intermediate e were coupled together to form a compound of Example 1 in a manner similar to that described for the alternative route to Example 1 above.



BINDING AND TRANSFECTION ASSAYS

Binding Assay:

Compounds were tested for their ability to bind to hPPAR gamma hPPARalpha or PPARdelta using a Scintillation Proximity Assay (SPA). The PPAR ligand binding domain (LBD) was expressed in E. coli as polyHis tagged fusion proteins and purified. The LBD was then labelled with biotin and immobilised on streptavidin-modified scintillation proximity beads. The beads were then incubated with a constant amount of the appropriate radioligand (5-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-thiazolidine-2,4-dione (*J.Med.Chem.* 1994, 37(23), 3977), for PPARgamma), and labelled GW 2433 (see Brown, P. J et al . *Chem. Biol., 4, 909-918 (1997)*, for the structure and synthesis of this ligand) for PPAR alpha and PPAR delta) and variable concentrations of test compound, and after equilibration the radioactivity bound to the beads was measured by a scintillation counter. The amount of nonspecific binding, as assessed by control wells containing 50 μM of the corresponding unlabeled ligand, was subtracted from each data point. For each compound tested, plots of ligand concentration vs. CPM of radioligand bound were constructed and apparent KI values were estimated from nonlinear least squares fit of the data assuming simple competitive binding. The details of this assay have been reported elsewhere (see, Blanchard, S. G. et. al. Development of a Scintillation Proximity Assay for Peroxisome Proliferator-Activated Receptor gamma Ligand Binding Domain. *Anal. Biochem., 257, 112-119 (1998)*).

Transfection assay:

Compounds were screened for functional potency in transient transfection assays in CV-1 cells for their ability to activate the PPAR subtypes (transactivation assay). A previously established chimeric receptor system was utilized to allow comparison of the relative transcriptional activity of the receptor subtypes on the same target gene

and to prevent endogenous receptor activation from complicating the interpretation of results. See, for example, Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkison, W. O.; Willson, T. M.; Kliewer, S. A., An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPARgamma), *J. Biol. Chem., 270, 12953-6 (1995)*. The ligand binding domains for murine and human PPAR alpha, PPAR gamma, and PPAR delta were each fused to the yeast transcription factor GAL4 DNA binding domain. CV-1 cells were transiently transfected with expression vectors for the respective PPAR chimera along with a reporter construct containing five copies of the GAL4 DNA binding site driving expression of secreted placental alkaline phosphatase (SPAP) and beta-galactosidase. After 16 h, the medium was exchanged to DME medium supplemented with 10% delipidated fetal calf serum and the test compound at the appropriate concentration. After an additional 24h, cell extracts were prepared and assayed for alkaline phosphatase and β-galactosidase activity. Alkaline phosphatase activity was corrected for transfection efficiency using the beta-galactosidase activity as an internal standard (see, for example, Kliewer, S. A., et. al. *Cell 83, 813-819* (*1995*)). Rosiglitazone (BRL 49653) was used as a positive control in the hPPAR gamma assay. The positive control in the hPPAR alpha assays was 2-4-[2-(3-[4-fluorophenyl]-1-heptylureido)ethyl]-phenoxy-(2-methyl propionic acid (WO 97/36579). The positive control for PPAR delta assays was 2-{2-methyl-4-[({4-methyl-2-{trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methyl)sulfanyl]phenoxy}acetic acid (WO 01/00603). The positive control was (5-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-thiazolidine-2,4-dione (*J.Med.Chem.* 1994, 37(23), 3977), for PPAR gamma.

Activities in three hPPAR subtypes are reported in the table and are expressed in micromolar.

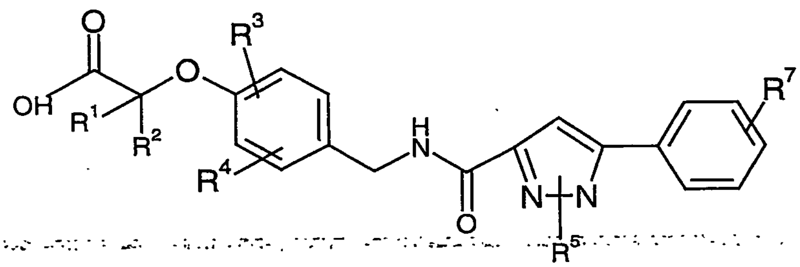
Example	EC50 μM HPPARα	EC50 μM HPPARδ	EC50 μM HPPARγ
Example 1	0.014	5.447	0.007
Example 2	0.018	0.820	0.044
Example 3	0.100	>10	0.212

Example 4	0.066	1.087	0.072
Example 5	0.301	>10	0.444
Example 7	0.002	2.060	0.008
Example 8	0.051	1.069	0.059
Example 10	2.895	>10	0.554
Example 11	0.050	2.166	0.029
Example 12	1.054	>10	0.432
Example 13	0.009	>10	0.011
Example 14	0.177	>10	0.130
Example 15	0.075	2.439	0.024
Example 16	0.163	10.000	1.090
Example 17	0.070	10.000	0.376
Example 18	0.004	4.021	0.009

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any novel feature or combination of features described herein. This may take the form of product, composition, process or use claims any include, by way of example and without limitation, one or more of the following claims.

What is claimed is:

1. A compound of formula (I) and pharmaceutically acceptable salts, solvates and hydrolysable esters thereof



(1)

R^1 and R^2 are independently H or C_{1-3} alkyl;
R^3 and R^4 are independently H, C_{1-6} alkyl, $-OC_{1-6}$ alkyl, halogen, OH, C_{2-6} alkenyl, CF_3
R^5 is H, C_{1-6} alkyl or CF_3,
R^7 is C_{1-6} alkyl (optionally substituted by one or more halogens), halogen, OC_{1-6} alkyl,

2. A compound according to claim 1 which is a selective hPPAR alpha/gamma agonist.

3. A compound according to claim 1 or 2 wherein R^1 and R^2 are independently C_{1-3} alkyl.

4. A compound according to claim 3 wherein R^1 and R^2 are both C_{1-3} alkyl.

5. A compound according to claim 4 wherein R^1 and R^2 are both methyl.

6. A compound according to claims 1 - 5 wherein R^4 is H.

7. A compound according to claims 1 - 6 wherein R^3 is $-C_{1-3}$ alkyl or $-OC_{1-3}$ alkyl

8. A compound according to claim 7 wherein R^3 is methyl or $-OCH_3$.

9. A compound according to claims 1 - 8 wherein R^3 is ortho to the depicted oxygen.

10. A compound according to claims 1 - 9 wherein R^3 is methyl.

11. A compound according to claims 1 - 10 wherein R^7 is C_{1-3} alkyl.

12. A compound according to claims 1 - 11 wherein R^7 is in the para position.

13. A compound according to claim 1 selected from

2-[(4-{[({5-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-methylphenyl)oxy]-2-methylpropanoic acid;
2-methyl-2-[(2-methyl-4-{[({1-methyl-3-[4-(1-methylethyl)phenyl]-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}phenyl)oxy]propanoic acid.
2-{[4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-(2-propen-1-yl)phenyl]oxy}-2-methylpropanoic acid.
2-[(4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-propylphenyl)oxy]-2-methylpropanoic acid;
2-{[4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}-2-methylpropanoic acid.
2-{[4-{[({5-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}-2-methylpropanoic acid.
2-methyl-2-[(2-methyl-4-{[({1-methyl-5-[4-(2-methylpropyl)phenyl]-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}phenyl)oxy]propanoic acid
2-methyl-2-[(2-methyl-4-{[({1-methyl-3-[4-(2-methylpropyl)phenyl]-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}phenyl)oxy]propanoic acid;
2-methyl-2-{[4-{[({1-methyl-5-[4-(1-methylethyl)phenyl]-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}propanoic acid;
2-methyl-2-{[4-{[({1-methyl-3-[4-(1-methylethyl)phenyl]-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}propanoic acid;
2-[(4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-methylphenyl)oxy]-2-methylpropanoic acid;
2-{[4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}-2-methylpropanoic acid;
2-[(4-{[({5-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-methylphenyl)oxy]-2-methylpropanoic acid;
2-methyl-2-{[4-{[({1-methyl-5-[4-(2-methylpropyl)phenyl]-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}-2-(methyloxy)phenyl]oxy}propanoic acid;
2-[(4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-ethyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}-2-methylphenyl)oxy]-2-methyl propanoic acid.

2-[(4-{[({3-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-5-yl}carbonyl)amino]methyl}phenyl)oxy]-2-methylpropanoic acid
2-[(4-{[({5-[4-(1,1-dimethylethyl)phenyl]-1-methyl-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}phenyl)oxy]-2-methylpropanoic acid.
2-methyl-2-[(2-methyl-4-{[({1-methyl-5-[4-(1-methylethyl)phenyl]-1*H*-pyrazol-3-yl}carbonyl)amino]methyl}phenyl)oxy]propanoic acid;

14. A compound according to claims 1 - 14 for use in therapy.

15. A pharmaceutical composition comprising a compound according to claims 1 - 14.

16. A pharmaceutical composition according to claim 15 further comprising a pharmaceutically acceptable diluent or carrier.

17. Use of a compound according to any of claims 1 - 14 for the manufacture of a medicament for the treatment of a hPPAR disease or condition.

18. Use according to claim 17 wherein the hPPAR mediated disease or condition is dyslipidemia, syndrome X, heart failure, hypercholesteremia, cardiovascular disease, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, obesity, anorexia bulimia and anorexia nervosa.

19. A method of treating a hPPAR mediated disease or condition in a patient comprising the administration of a therapeutically effective amount of a compound according to claims 1 - 14.

20. A method according to claim 19 wherein the hPPAR mediated disease or condition is dyslipidemia, syndrome X, heart failure, hypercholesteremia, cardiovascular disease, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, obesity, anorexia bulimia and anorexia nervosa.

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